American Heart Journal

An international publication for the study of the circulation

VOLUME 93

JANUARY-JUNE 197

American Heart Journal

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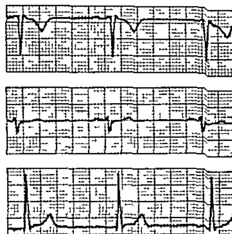
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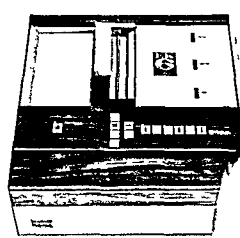
More diagnostic accuracy: three views of every heartbeat, simultaneously.

New Burdick EK 6 3 channel electrocardiograph—During periods of cardiac instability more accurate diagnosis demands more complete data Having that information in seconds is one reason you should have *the new Burdick EK 6 3-channel electrocardiograph*

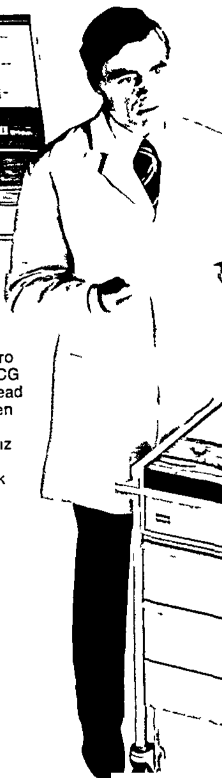
The EK 6 gives you three different perspectives of the heart all at once You can perceive the status of the *heart more accurately with recording flexibility that is* critical for complete cardiac diagnosis



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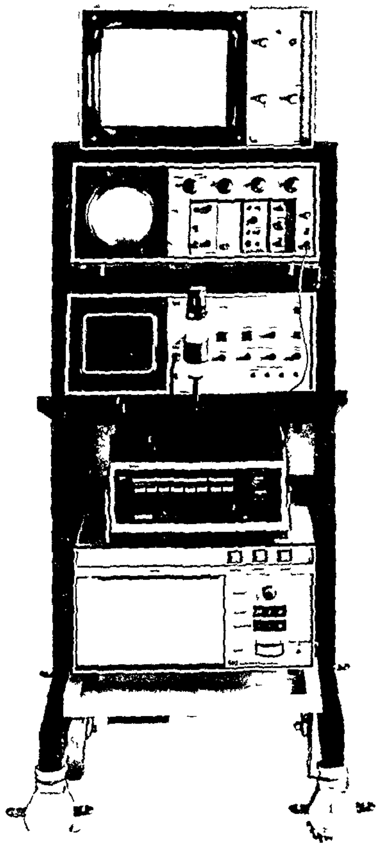
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If you already own the world's leading echocardiography unit you don t need to buy a whole new system for two-dimensional heart scanning

Our new EkoSector I is completely compatible with existing Ekoline 20A® s which means your expenditure for the system can be cut almost in half

SKI s new EkoSector I offers you real time cross sectional scanning in a fully integrated system

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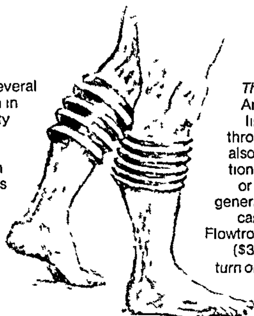
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Deep vein thrombosis is a preventable complication of surgery.



Cutting into the human body triggers several hemostatic mechanisms including an increase in blood coagulation factor activity While the post surgical patient is bed ridden this hypercoagulability sometimes causes clotting in blood pooled in the major muscles of the lower limbs This is deep vein thrombosis and it can be avoided in the vast majority of patients by preventing blood pooling and reducing the defensive hyper *coagulability triggered by surgery*

A *safe non invasive* physical technique has been developed in Europe to simultaneously improve lower limb circulation and increase the bodys natural fibrinolysis This technique is *pneumatic intermittent compression* (p i c) a physical simulation of the act of walking

During walking the calf muscles alternately compress the right and left lower leg venous masses This intermittent compression is accurately simulated by the firm alternating pressure of the *Berkeley Flowtron pneumatic intermittent* compression system The benefits of p i c include both elimination of pooling (1 2 3) and stimulation of fibrinolysis (4 5)

The human body was designed to be ambulatory And the benefits of simulated ambulation are not limited to prevention of post surgical deep vein thrombosis Pneumatic intermittent compression is also a safe non invasive technique for the prevention or reduction of edema associated with venous or lymphatic insufficiency (6) The circulation and general physical well being of any bedridden patient can benefit from daily therapy with the Berkeley Flowtron system and the device is inexpensive enough ($395) simple enough (slip on boots or arm cuffs turn one knob) *and quiet enough (virtually inaudible)* to be applied during nursing home or at home convalescence from major surgery

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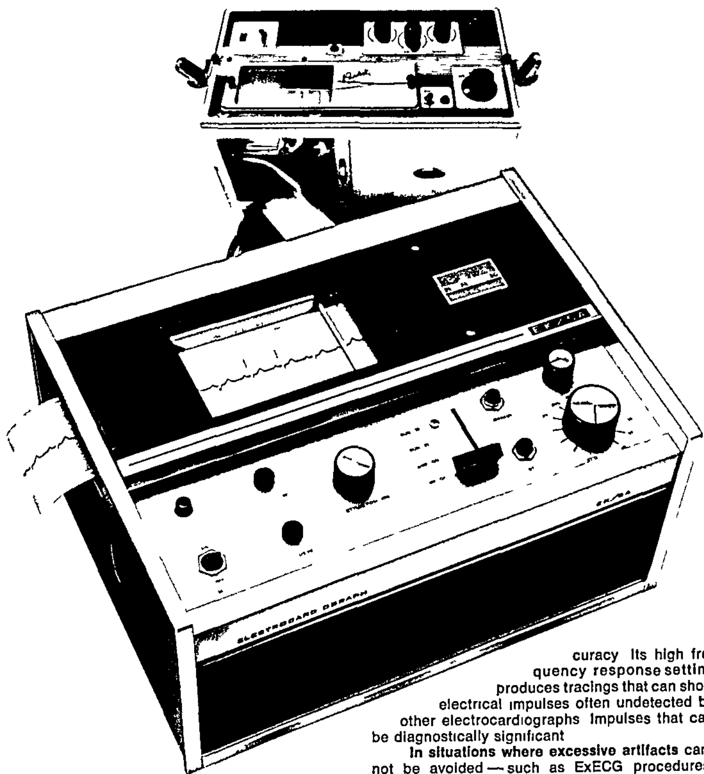
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Why your old cardiograph can't match our new one.



Innovations Technical innovations in electrocardiography that make your old cardiograph whatever its condition virtually obsolete if it s more than 7 years old Innovations that are incorporated into the *design* and construction of the Burdick EK-5A

The solid state EK 5A exceeds the minimum AHA frequency response recommendations Its unique rectilinear recording process produces high fidelity ECG s with exact definition and accuracy Its high frequency response setting produces tracings that can show electrical impulses often undetected by other electrocardiographs Impulses that can be diagnostically significant

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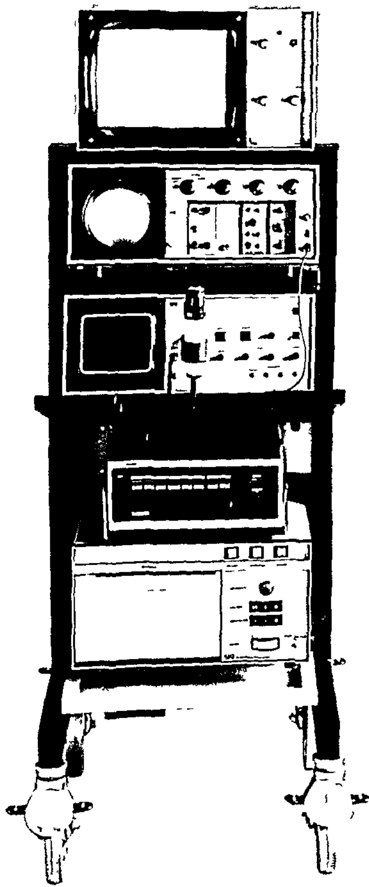
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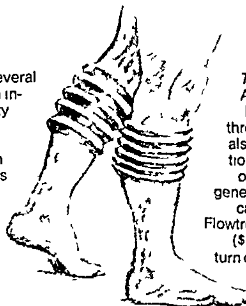
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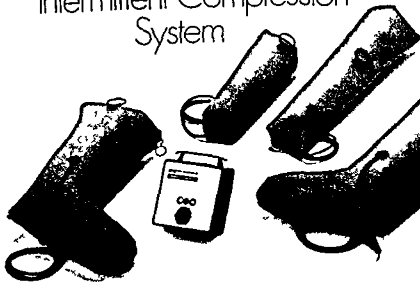
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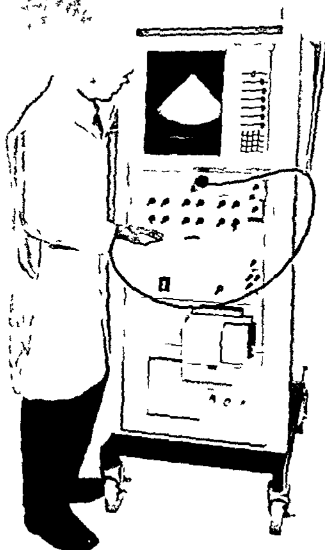
The V 3000 establishes
the fast growing field
This instrument

such as adult

The V-3000 scans an 80 degree two-dimensional section at 30 *frames per second* When the transducer is positioned to direct the ultrasound beam between the patient s ribs it can give an unobstructed field of view large enough to image the entire left ventricle of an average adult heart Or, *moved freely* across the abdomen the same trans ducer produces instantaneous high resolution images permitting a fast yet meaningful ultrasonic examination the ultrasonic *equivalent to fluoroscopy*

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V-3000
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The Story Behind The Venturi Principle And Our System *The principle actually started before Venturi himself* Dr Daniel Bernoulli formulated the basic theory on gas and fluid kinetics in 1738

It wasn t until 1791 that G B Venturi—using Bernoulli s Law—formulated his principle to measure and regulate gas and *liquid flow*

G B VENTURI 1746 1822

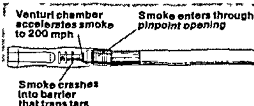
The principle s first practical application came in 1886 when *an American* engineer Clemens Herschell developed the Venturi Tube It wasn t long before the Venturi Tube was used in medicine—in bedside aspirators for critical respiratory management for *example*

The Venturi Principle was first applied to cigarette smoking in 1963 with the development of the TAR GARD® cigarette filter/holder TAR GARD® holders help reduce the tar and nicotine intake of smokers who can t or won t stop smoking Several years after the TAR GARD® approach was used to help pipe smokers as well

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Smoke entering a Venturi holder accelerates to over 200 mph before it *crashes into a barrier There harmful high* temperature tars and nicotine precipitate and collect



Each Venturi cigarette holder is used for one week The first holder removes 15% of the tars and nicotine from the smoke stream the second—30% the third—65% the fourth—95% By the end of the fourth week the patient is one short step away *from stopping*

Things Your Patients Should Know About Smoking

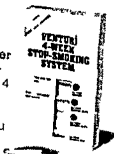
Cigarette smoking is truly an addiction The confirmed smoker suffers under a craving and compulsion like that of a drug addict

Smoking tobacco is essentially a way to inject nicotine into the body

Nicotine is a colorless oily compound which in concentration is one of the deadliest poisons known In fact a 70 mgs injection can cause death within a few minutes

Nicotine poisoning symptoms include dizziness rapid pulse cold and clammy skin nausea and vomiting Habitual smokers may sometimes experience these symptoms and attribute them to other causes

Aside from the hazards of nicotine addiction smoking exposes your patients to carcinogens Smokers are also more prone to cardiovascular and *respiratory diseases*



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To introduce you and your patients to the Venturi System we re offering Venturi *Systems at a special professional price* Each system contains 4 Venturi holders—phases 1 through 4 a program that tells patients what to expect and what to do plus guidelines on how to quit for good after the 4th Venturi week

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American Heart Journal

January 1977 Volume 93, Number 1

Editorial

Arteriosclerotic heart disease and surgical risk

Joseph L. Ponka M D
Detroit Mich

Physicians and surgeons are well aware of the fact that patients with heart disease represent increased risks when exposed to a variety of operative procedures Precisely what disease states account for such increased hazards is a practical question which deserves an answer Surgeons are concerned about the status of the patient s cardiac function and reserve They manifest such uneasiness by well directed consultation requests to cardiologists and internists with particular ability to evaluate the *functional* state of the heart

There has been a gradual increase in the number of older patients requiring surgical treatment As recently as 25 years ago we were reluctant to operate upon patients who were 60 years of age Currently we are often called upon to operate upon patients in their seventh eighth and even ninth decades of life With advancing age patients unfortunately acquire a number of neoplastic degenerative and metabolic diseases Burch appropriately pointed out that when dealing with aged patients broad knowledge of medicine and wide experience with them teaches us that elderly patients frequently suffer from numerous other diseases *in addition* to their cardiac disorders Of all diseases afflicting aged patients arteriosclerotic cardiovascular diseases take the heaviest toll Because of the frequency of arteriosclerotic heart disease in our patients we decided to carry out a statistical study of heart disease as a risk factor in old patients

We directed our attention to 416 patients with documented arteriosclerotic heart disease during the year 1970 at Henry Ford Hospital These were then divided somewhat arbitrarily into 5 groups as follows preoperative myocardial infarction (uncomplicated) 111 patients preoperative angina (normal ECG) 99 patients both angina and history of infarction 55 patients preoperative myocardial infarction (complicated) 61 patients and arrhythmia or congestive heart failure without myocardial infarction 90 patients

We found that patients who had suffered a myocardial infarction in the past but who had recovered to a well compensated state tolerated anesthesia and operative procedures remarkably well In this group the complication rate was 6 per cent the mortality rate was 2 8 per cent

Patients who recovered from myocardial infarction but who continued to have anginal attacks showed a significantly greater number of complications (14 per cent) and mortality (11 per cent)

With a history of myocardial infarction followed by cardiac arrhythmia congestive heart failure or evidence of ischemic changes on electrocardiography cardiorespiratory complications occurred in nearly one half of the individuals

In 38 patients with severe A V block pacemakers were inserted *prior* to operation We found this to be essential before performing procedures on patients with bilateral bundle branch block or a Mobitz II or third degree A V

From the Department of Surgery Fourth Surgical Division, Henry Ford Hospital, Detroit Mich.

Received for publication Feb 6, 19 6.

Reprint requests to Joseph L. Ponka M D Chief Fourth Surgical Division, Henry Ford Hospital, 2799 W Grand Blvd Detroit Mich 48202.



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In 38 patients with severe A V block pacemakers were inserted prior to operation We found this to be essential before performing procedures on patients with bilateral bundle branch block or a Mobitz II or third degree A V

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Clinical communications

Systolic mitral flutter: an echocardiographic clue to the diagnosis of ruptured chordae tendineae

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Echocardiography has proved useful in helping to establish the diagnosis of mitral regurgitation due to ruptured chordae tendineae. Other investigators[1] have described features of this entity which in the proper clinical setting may be diagnostic prior to cardiac catheterization or surgery. However, all of these features may not be present in a given patient. Also, there is significant variability in echocardiographic technique and interpretation. For example, there may be difficulty in distinguishing mitral regurgitation with ruptured chordae tendineae from that of pansystolic prolapse of the mitral leaflets with redundant chordae. Also, previously described diastolic flutter of the mitral valve may be confused with that seen in patients with aortic regurgitation. Thus we shall describe a new finding of mitral leaflet systolic flutter which by itself may be diagnostic of chordal rupture.

Two patients with systolic flutter are illustrated here. One had pathological proof of ruptured chordae tendineae and the other had strong presumptive evidence for it. The echocardiograms of 75 patients with mitral regurgitation due to other causes were reviewed for comparison. Systolic flutter was not present on any of the tracings.

Both patients were examined with a Unirad series C Echocardiography System utilizing a 2.0 MHz ⅝ diameter crystal transducer. Permanent records were made on a Techtronics strip chart recorder utilizing a fiber optic line printer at a paper speed of 50 mm. per second. Standard views to include the mitral valve, the ventricular septum, and the posterior left ventricular wall were obtained. The patients were examined in a semirecumbent position (torso elevated to approximately 30°).

Case reports

Case 1. L. M., a 44-year-old black man, was admitted to the George Washington University Hospital on June 15, 1974, after a syncopal episode. There was a vague history of fever, chills, night sweats, and malaise for approximately 1 month prior to admission. He complained of progressive shortness of breath and paroxysmal nocturnal dyspnea for 2 weeks prior to entry. He had a past history of heavy alcohol consumption with biopsy-proved Laennec's cirrhosis at another hospital.

Physical examination revealed a cachectic middle-aged man in moderately severe respiratory distress. The blood pressure was 95/70 mm. Hg, the pulse was 96 and regular, and the temperature was 38.5° C. The neck veins were distended to 8 cm. above the sternal angle in the upright position; the carotid pulses were brisk. A hyperkinetic apical impulse was palpated at the anterior axillary line and a left parasternal heave was present. S_2 was normally split but P_2 was accentuated. A prominent pansystolic crescendo-decrescendo murmur was heard at the apex, the axilla, and over the spine. An S_3 and an S_4 followed by a diastolic flow rumble were present at the apex.

Echocardiographic examination (Fig. 1A) showed exaggerated excursion of the anterior mitral leaflet (45 mm.), the ventricular septum (13 mm.), and the posterior left ventricular wall (19 mm.) in addition to left atrial enlargement (5.9 cm.). The anterior leaflet exhibited coarse diastolic flutter motion and appeared to touch the septum. There appeared to be two major tracings of the anterior leaflet—one with normal excursion and the other with exaggerated motion—a nonparallel double image. An additional new finding was the presence of fine systolic fluttering of the anterior mitral leaflet (Fig. 1B).

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block Two patients with severe A V block who required major operations, but who were not protected with pacemakers died postoperatively of arrhythmias

These patients underwent 169 diagnostic and 255 therapeutic procedures Local anesthesia was selected for 262, general anesthesia for 117, and spinal anesthesia for 45 patients The procedures performed varied greatly in magnitude, some being of a diagnostic nature Nevertheless over one half of the procedures were of a major nature such as, thoracotomies laparotomies orthopedic and vascular operations, and intracranial and head and neck operations

In general, patients with arteriosclerotic heart disease can tolerate necessary surgical operations under local anesthesia with a low mortality rate of approximately one per cent Even patients who have recovered from myocardial infarction tolerate required procedures very well Morbidity and mortality rates increase rapidly in those individuals who have had myocardial infarction and who continue to have angina, evidence of heart failure arrhythmia bundle branch block and ischemic changes on ECG studies Patients with recent myocardial infarction represent grave risks since the mortality rates following necessary operative procedures may be as high as 90 per cent

REFERENCES

1 Burch G E Interesting aspects of geriatric cardiology AM HEART J 89 99 1975
2 Sapala J A Ponka J L and Duvernoy W B C Operative and nonoperative risks in the cardiac patient J Am Geriatr Soc 23 529 1975

Clinical communications

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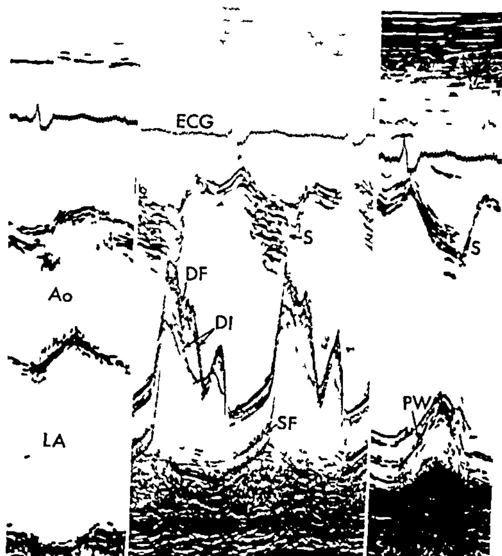


Fig 1A Echocardiogram of Patient 1 showing exaggerated motion of the anterior mitral leaflet and nonparallel double image of the anterior leaflet (*DI*) coarse diastolic flutter of the anterior leaflet (*DF*) exaggerated motion of the septum (*S*) and posterior left ventricular wall (*PW*) and the new finding of systolic flutter (*SF*)

The differential diagnosis as to the etiology of his heart disease was mainly between congestive alcoholic cardiomyopathy with secondary severe mitral regurgitation and primary mitral regurgitation with rupture of chordae tendineae possibly secondary to infective endocarditis Vigorous motion of the ventricular septum the posterior left ventricular wall and the anterior mitral leaflet made the diagnosis of congestive cardiomyopathy unlikely These findings in conjunction with diastolic flail motion and fine systolic fluttering from the anterior mitral leaflet strongly suggested ruptured chordae tendineae as the etiology for mitral regurgitation

During the patient s hospitalization no specific etiology for either syncope or fever was discovered A total of 12 blood cultures obtained on admission were all negative for bacterial growth However the patient was treated for bacterial endocarditis for 6 weeks with 12 million units of penicillin G intravenously and 1 Gm of streptomycin intramuscularly per day In the last week of the hospitalization cardiac decompensation occurred but he responded well to a low sodium diet digitalis and diuretics

He was readmitted on Sept 17 1974 because of recurrent attacks of paroxysmal dyspnea Physical findings were not significantly changed except for the presence of bilateral basilar râles A repeat echocardiogram showed no remarkable changes.

Findings of cardiac catheterization done on Oct 21 1974 were (1) markedly elevated pulmonary capillary wedge pressures with a wave of 45 mm v wave of 75 mm and a mean of 35 mm (2) severe pulmonary hypertension with a main pulmonary artery pressure of 105/37 (mean 57) (3) 4+ mitral regurgitation with good ventricular contractility on left ventricular angiogram

On Nov 1 1974 open heart surgery was performed with mitral valve replacement by a porcine heterograft At the time of surgical repair the chordae tendineae attached to the central portion of the anterior mitral leaflet were torn (Fig 2) The posterior leaflet chordae were intact Multiple small white excrescences were scattered over the leaflets Possibly they represented vegetations although no organism was cultured from the valve The patient has done well subsequent to surgery

Case 2 S W a 22 year old black woman was admitted to the George Washington University Hospital on Sept 29 1974 because of cardiac decompensation

She experienced acute rheumatic fever in August 1971 She

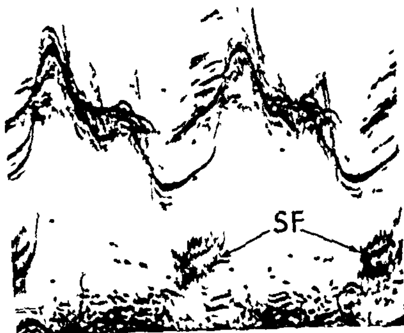


Fig 1B Magnified echocardiographic image of the mitral valve in Patient 1 demonstrating the fine systolic flutter (*SF*) of the anterior mitral leaflet with a frequency of 82 Hz

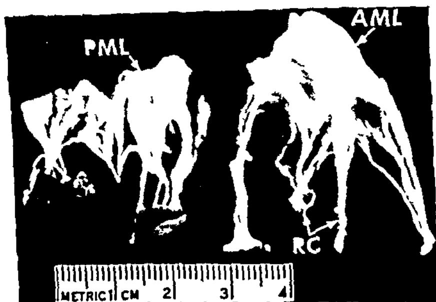


Fig 2 Surgical specimen of mitral valve of Patient 1 The chordae tendineae attached to the posterior mitral leaflet (*PML*) and to the lateral aspects of the anterior mitral leaflet (*AML*) were intact but those to the central *AML* were ruptured (*RC*)

was admitted to GWUH in March 1973 after a ? month history of progressive congestive heart failure Pertinent physical findings were an apical presystolic rumble of mitral stenosis and a prominent pansystolic murmur of tricuspid regurgitation along the left sternal border The second sound was widely split with marked accentuation of P Echocardiographic examination revealed a slightly thickened mitral valve with E F slope of 22 mm per second and anterior leaflet excursion of 25 mm (Fig 3) Cardiac catheterization findings were (1) severe mitral stenosis with mean diastolic gradient of 15 mm across the mitral valve ( ) moderately severe pulmonary hypertension with main pulmonary artery pressure of 75/50 (mean 60) (3) no mitral regurgitation

On Sept 13 19 3 a closed mitral commissurotomy was performed Immediately following surgery a new apical high pitched holosystolic murmur was heard The patient did well

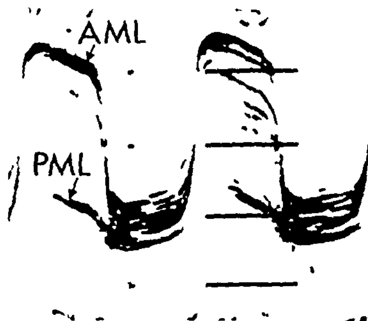


Fig 3 Preoperative echocardiographic tracing of mitral valve in Patient 2 Excursion of anterior mitral leaflet (*AML*) is 25 mm and diastolic slope is 22 mm per second Posterior mitral leaflet (*PML*) moves anteriorly with diastole

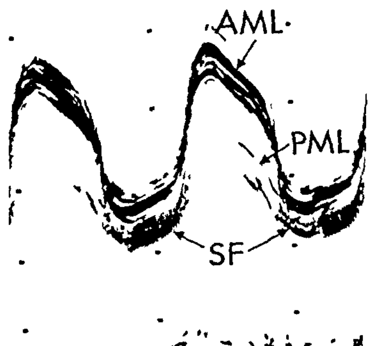


Fig 4 Post commissurotomy echocardiographic tracing of mitral valve in Patient 2 Diastolic slope of anterior mitral leaflet (*AML*) has increased to 40 mm per second posterior mitral leaflet (*PML*) continues to move anteriorly with diastole Fine systolic flutter (*SF*) with a frequency of 125 Hz has developed

postoperatively while on digitalis diuretics and oral penicillin prophylaxis However she was readmitted to the hospital on Sept 29 1974 when congestive heart failure ensued after an upper respiratory infection She was treated with bedrest digitalis and diuretics with marked improvement in her condition

On physical examination the patient was a young thin woman without dyspnea The pulse was 75 and regular the blood pressure was 105/70 mm Hg and the temperature was 37 0° C The neck veins (at 45°) were distended to the angle of the mandible and pulsated with systole The lungs were normal to auscultation and percussion Cardiac examination revealed the apical impulse at the anterior axillary line with a systolic thrill A prominent left parasternal heave was present The second heart sound was again widely split with a prominent P_2 A Grade 4/6 high pitched musical holosystolic murmur was heard over the apex and into the back The same Grade 3/6 holosystolic murmur along the left sternal border was present An S and an S followed by a short diastolic rumble were present at the apex

Echocardiographic examination revealed improved E F slope of 40 mm per second (Fig 4) and a striking new finding of fine systolic fluttering of the anterior leaflet of the mitral valve

Pertinent findings from cardiac catheterization done on Oct 7 1974 were (1) left atrial pressures of a wave 30 v wave 46 with mean of 38 (2) mean diastolic gradient of 11 mm across the mitral valve (3) pulmonary hypertension with main pulmonary artery pressure of 80/50 (mean 63) (4) 3+ mitral regurgitation in the form of an eccentric jet into the left atrium of left ventricular angiography

In view of the clinical course angiographic findings and pressure data findings the cause of the patient s mitral regurgitation is most likely surgical rupture of chordae tendineae The patient remained in mild congestive heart failure subsequent to catheterization

Discussion

The echocardiographic features of mitral regurgitation with ruptured chordae tendineae of the posterior mitral leaflet are varied They include (1) *echoes within the left atrium from* flail chordae tendineae or from the prolapsed posterior leaflet[1 3 6] (2) absence of coaptation of the mitral leaflet during systole, representing a form *of prolapse*[1 5 7] *(3) multiple systolic echoes from* the leaflets, directed posteriorly with a hammock like appearance[4 7] (note findings 2 and 3 can be seen with ruptured chordae from either leaflet) (4) paradoxical anterior *diastolic motion* from a flail posterior leaflet[4 7]

In anterior leaflet chordal rupture there may be (1) increased excursion of the anterior leaflet such that it appears to touch the ventricular septum in early diastole[1 4] (2) a rapid rate of leaflet opening[4] and (3) a characteristic chaotic fluttering of the leaflet in diastole[2]

With ruptured chordae tendineae of either or both leaflets usually there are (1) vigorous motion of the ventricular septum to produce an increased stroke volume[1] and (2) exaggerated systolic excursion of the left atrial wall[4]

Case 1 demonstrated coarse diastolic flutter of the anterior leaflet and exaggerated motion of

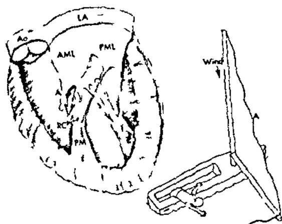


Fig 5 Highly schematized frontal section of the left ventricle (left) with comparable aerodynamic circumstance (right) The coarse diastolic flutter of the untethered edge of the mitral leaflet (*A*) in diastole due to ruptured chordae tendineae (*RC*) is analogous to the luffing of a sail turned loose in the wind Note that blood flow is parallel to the leaflet just as the wind is parallel to the sail

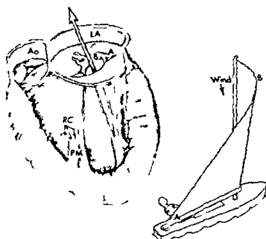


Fig 6 The fine high frequency flutter of the untethered edge of the mitral leaflet (*B*) which is partially pulled (*A*) into the jet of regurgitation is similar to the vibration of a sail loose leach (*B*) when its lower position is close hauled (pulled in tight) (*A*) Blood flow is perpendicular to the leaflet just as the wind is nearly perpendicular to the sail

both the ventricular septum and the anterior leaflet such that they appeared to touch in early diastole In addition to these features fine systolic leaflet fluttering was observed Unless separation of the leaflets is seen it is not possible echocardiographically to distinguish the anterior and posterior leaflets in systole This fluttering involved the anterior leaflet margin since its chordae were found to be ruptured at the time of surgery Regardless of the particular leaflet the systolic flutter was a characteristic reproducible finding

Our patient and previous studies have demonstrated diastolic fluttering of the anterior leaflet An analogy to a flapping sail in the wind"[2] is appropriate The dynamics of the diastolic flapping and the systolic flutter are quite different The diastolic flutter is caused by low velocity blood flow across the flail leaflet in a parallel direction much the same as a sail *luffing* in a breeze (sail turned loose) (Fig 5) The systolic flutter however is the result of a high velocity jet of blood across the leaflet margin which is perpendicular to the flow This is analogous to a sail close hauled bottom edge (pulled tightly) into a strong wind with the leach (free edge) of the sail loose This results in a higher frequency less chaotic flutter (Fig 6)

Case 2 demonstrated the unique finding of systolic mitral flutter as the only clue to ruptured chordae tendineae Although this diagnosis has not been made pathologically severe mitral regurgitation developing immediately *following* commissurotomy and an eccentric jet of regurgitation on left ventricular angiography make the diagnosis highly tenable The other echocardiographic findings of ruptured chordae tendineae may be inhibited in a valve previously thickened and noncompliant by rheumatic heart disease This makes the *systolic flutter of* particular diagnostic *importance* in such patients

Because the systolic flutter had never been previously noted the echocardiograms of 75 patients with mitral regurgitation due to causes other than ruptured chordae tendineae were reviewed This finding was not seen on any of the tracings

Mitral valve systolic flutter has been mentioned incidentally by Nanda and associates in three patients with mitral valve prolapse It is noteworthy that as common as mitral prolapse is all three patients in whom systolic mitral flutter was seen had had subacute bacterial endocarditis It is probable that these patients have associated *rupture* of the chordae tendineae secondary to the bacterial *infection*

It is not difficult to see why this finding has not been described previously The flutter occurs at a very high frequency The flutter frequency in case

1 was 82 Hz and that in case 2 was 125 Hz, whereas the flutter frequency in diastole in case 1 was 21 5 Hz Therefore, detection of this finding requires a recording device with high resolution and high frequency recording characteristics as are seen in most of the new continuous strip chart recorders

The echocardiographic diagnosis of ruptured chordae tendineae may be of vital importance to those caring for a critically ill patient The finding of systolic fluttering of a mitral leaflet not only may help to establish the diagnosis in combination with the other echocardiographic signs but may be the only echocardiographic finding as in case 2 It appears to be quite specific for this condition

Summary

A new finding of fine systolic fluttering of the mitral leaflet is described in two patients with ruptured chordae tendineae and severe mitral regurgitation The flutter is caused by the action of high velocity blood flow upon the leaflet margin that has lost its support The jet stream of blood evokes a high frequency vibratory motion of the tensed leaflet as opposed to the previously described, lower frequency less specific diastolic flutter This finding was not seen in the echocardiograms of 75 patients with other forms of mitral regurgitation Systolic flutter appears to be specific for ruptured chordae tendineae

Addendum

Since submission of this report for publication we have encountered three additional patients exhibiting high frequency pansystolic mitral flutter Two patients were men with ruptured chordae tendineae secondary to bacterial endocarditis documented at surgery The third patient is a 64 year old woman with recent onset of mitral regurgitation and congestive heart failure The diagnosis of chordal rupture appears likely in this patient but not proved These additional cases suggest that this finding is not uncommon in patients with ruptured chordae tendineae

We are grateful to Miss Teresa Green for her assistance in preparation of the manuscript

REFERENCES

1 Sweatman T Selzer A Kamagaki M and Cohn K Echocardiographic diagnosis of mitral regurgitation due to ruptured chordae tendineae Circulation **46** 580 1972
2 Duchak J M Chang S and Feigenbaum H Echocardiographic features of torn chordal tendineae Am J Cardiol **29** 260 1972
3 Millward D K McLaurin L P and Craige E Echocardiographic studies of the mitral valve in patients with congestive cardiomyopathy and mitral regurgitation AM HEART J **85** 413 1973
4 Burgess J Clark R Kamignki M and Cohn K Echocardiographic findings in different types of mitral regurgitation Circulation **48** 97 1973
5 Sasse L Lightfoot P Burgess I Clark R and Cohn K Echocardiography of mitral valve prolapse (letter) Circulation **49** 595 1974
6 Giles T Burch G and Martinez E Value of exploratory scanning in the echocardiographic diagnosis of ruptured chordae tendineae Circulation **49** 678 1974
7 DeMaria A King I Bogres H Fries I and Mason D The variable spectrum of echocardiographic manifestations of the mitral valve prolapse syndrome Circulation **50** 33 1974
8 Wexler L Silverman J F DeBusk R F and Harrison D C Angiographic features of rheumatic and non rheumatic mitral regurgitation Circulation **44** 1080 1971
9 Nanda N C Gramiak R and Manning J A Echocardiography of the tricuspid valve in congenital left ventricular right atrial communication Circulation **51** 268 1975

Effects of contrast medium on left ventricular pressure and volume with emphasis on coronary artery disease

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Studies in both man and animals[1] indicate that the injection of angiographic contrast medium into the circulation is accompanied by significant hemodynamic alterations which include altered blood volume myocardial depression and decreased peripheral vascular resistance Clinical studies [7] have indicated that after the injection of angiographic contrast media there are significant increases in the left ventricular end diastolic pressure cardiac output and stroke volume Such hemodynamic changes have been utilized by some[11] [1] to assess valvular heart disease and by others [2] [17] to evaluate left ventricular function in coronary artery disease Left ventricular function has been evaluated by relating the changes of the left ventricular end diastolic pressure which accompany the injection of contrast media to the stroke work [2] It is uncertain whether the changes observed in the left ventricular end diastolic pressure after the injection of angiographic material are due to direct myocardial depression [1] or due to altered preload as a result of a transient increase in circulating blood volume It would appear that before one can interpret the relationship between end diastolic pressure and stroke work after the injection of contrast medium an evaluation of the volume changes of the left ventricle accompanying changes in filling pressure is required The following investigation was designed to determine whether the injection of contrast material is associated with changes in left ventricular volume

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Methods

Two methods were used to evaluate the effect of contrast material on left ventricular pressure and volume Duplicate left ventricular angiograms were performed on 41 patients during a diagnostic evaluation and seven patients with radiopaque epicardial markers attached to the left ventricle during previous aortocoronary bypass surgery were studied postoperatively

Angiographic study Forty one patients had duplicate angiographic studies Seven patients were evaluated because of angina like pain and were found to have normal coronary angiograms and normal left ventricular function The latter included a normal cardiac output left ventricular end diastolic pressure end diastolic volume ejection fraction and a normal contractile pattern All seven of these patients had a normal electrocardiogram (ECG) and were designated as the normal group The remaining 34 patients were referred because of angina pectoris and were documented on selective coronary angiography to have significant coronary artery disease No patient had main left coronary artery disease These 34 patients were divided into three groups depending on the number of vessels involved with significant coronary artery disease Single vessel disease was present in 10 patients with four of the patients having ECG evidence of transmural myocardial infarction Double and triple vessel

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7 DeMaria A King I Bogres H Fries I and Mason D The variable spectrum of echocardiographic manifestations of the mitral valve prolapse syndrome Circulation 50 33 1974
8 Wexler L Silverman J F DeBusk R F and Harrison D C Angiographic features of rheumatic and non rheumatic mitral regurgitation Circulation 44 1080 1971
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Table I Observations of duplicate angiographic studies

	Normal group		Arteriosclerotic heart disease group: Single vessel disease		Double vessel disease		Triple vessel disease	
	A	B	A	B	A	B	A	B
Number	7		10		10		14	
Age (yr)	43 ± 8		44 ± 9 4		50 ± 6 0		52 ± 8	
Sex (M/F)	5/2		10/0		10/0		14/0	
End systolic volume (ml)	40 ± 15	43 ± 16	47 ± [illegible]1	56 ± 24	70 ± 29	77 ± 39	61 ± 34	74 ± 44
End-diastolic volume (ml)	140 ± 30	165 ± 46	13[illegible] ± [illegible]	161 ± 28	149 ± 39	174 ± 45	149 ± 4[illegible]	175 ± 48
Stroke volume (ml)	100 ± 24	12[illegible] ± 25	88 ± 16	105 ± 17	79 ± 14	96 ± 27	87 ± 29	101 ± 35
Ejection fraction	0 71 ± 0 05	0 74 ± 0 06	0 6[illegible] ± 0 10	0 65 ± 0 11	0.53 ± 0 09	0.55 ± 0 14	0.59 ± 0 14	0.58 ± 0 14
Heart rate (beats per minute)	72 ± 11	75 ± 6	80 ± 13	80 ± 13	84 ± 17	81 ± 16	69 ± 10	[illegible]0 ± 13
Left ventricular systolic pressure (mm Hg)	127 ± 17	135 ± 13	130 ± 16	145 ± 17	160 ± 26	163 ± 22	136 ± 22	142 ± 14
End-diastolic pressure (mm Hg)	9 ± 1 0	13 ± 2 2	10 ± 4 1	18 ± 5 4	13 ± 5 1	25 ± 6 8	12 ± 4 1	[illegible]4 ± 7.5

A = Observ tions noted on the first angiograph study B = *observ tio noted on the second* angiographic study All values represent means and ± 1 sta dard deviation

nous bypass grafts were performed to both the anterior and posterior descending arteries and radiopaque epicardial clips were placed slightly to the left of the anterior *posterior interventricular* grooves just adjacent to the distal anastomotic site It was assumed that *the* distance between these two epicardial clips *approximated the trans verse diameter* of the heart and was a reliable indicator for evaluating the relative *changes in* the size of the heart during both systole and diastole The value and safety of epicardial markers in studying changes in cardiac dimen sions in man have been previously demon strated Others have used epicardial clips as an adjunct to evaluate *patients during the early* postoperative course after open heart surgery Approximately 2 *weeks after* aortocoronary bypass surgery all seven patients underwent *postoperative* evaluation which is routinely performed at this institution after bypass surgery At the time of study one catheter was placed percutaneously through the femoral artery into the left ventricle and a pacemaker catheter passed percutaneously was placed in the right atrium A cinegraphic clip study was performed st prior to and 1 3 5 10 and 15 minutes after e left ventricular angiogram At the completion the study *selective saphenous* vein bypass igiogram was performed In all seven patients ie preangiographic end diastolic pressure as well as the left ventricular end diastolic volume ejection fraction and *contractile pattern were* normal All saphenous vein grafts were patent *For each cinegraphic* clip study the patient was *placed in a* right anterior oblique projection at an angle which demonstrated maximum separation *of the* epicardial clips and the patient remained in this position for the entire study During each *study* right atrial pacing was *performed at a rate* slightly above the sinus rate to guarantee a constant heart rate for the entire study Just prior to obtaining the cinefluorogram the left ventric *ular end* diastolic pressure was recorded Cine fluorograms were then obtained at the time inter *vals noted* during inspiration The cine films were analyzed with a 35 mm projector A continuous measurement of the intraclip distance was obtained with an electronic *digitizer interfaced* to a digital computer and X Y plotter In this *manner* an on line continuous plot of the intra clip distance was obtained The end diastolic intraclip measurement was taken between 40 and 60 msec after the onset of the QRS and the mean value of five consecutive cycles for each time interval was utilized

Results

Angiographic study The left ventricular pres sures volumes and *ejection* fraction for the initial angiographic study (Study A) and for that

disease was present in 10 and 14 patients, respectively Three patients with double and six patients with triple vessel disease had electrocardiographic evidence of prior transmural myocardial infarction

Cardiac catheterization was performed in the fasting state by methods routinely utilized in this laboratory and consisted of right and transseptal combined with retrograde left heart catheterization The normal left ventricular end diastolic pressure for this laboratory is 11 mm Hg or less Left ventricular angiograms were obtained in the right anterior oblique position by injecting 0 50 to 0 75 ml per kilogram of 90 per cent sodium meglumine diatrizoate into the left atrium or left ventricle over 2 seconds with a power injector (Viamonte Hobbs) Two angiographic studies were performed in each patient The first angiographic study was designated Study A and was followed in 3 minutes by a similar angiographic study designated Study B The 3 minute interval between the angiographic study was chosen because of previous observations by others[11 13 16] indicating that the maximum increase in the left ventricular end diastolic pressure noted after an angiogram occurred 2 to 4 minutes after the injection of contrast medium Just prior to each left ventricular angiogram the left ventricular pressure, at both high and low gain sensitivity was recorded During both studies (A and B) no patient had an arrhythmia or complained of chest pain The extra study (Study B) performed on each patients added about 5 minutes to the entire procedure Each patient was given an explanation of the procedure and informed consent was obtained Cineangiograms were taken with a 35 mm camera at 60 frames per second A tracing of Lead II of the ECG was superimposed in the right upper corner of each cine frame (Cinetrace Electronics for Medicine) The x ray equipment utilized for the study as well as the epicardial marker study included a dual field 6 inch 3 000 gain 9 inch 6 000 gain image intensifier (General Electric) with a 35 mm (Photomechanism) synchronous camera utilizing a grid control x ray tube After the completion of Study B a grid of known dimension was positioned at the approximate location of the left ventricle and a short film strip taken to permit correction due to magnification After the completion of the duplicate left ventricular angiographic study, selective coronary angiograms were performed

Left ventricular volumes were obtained by the area length method[19] and regression equation of Kasser and Kennedy[0] The cine films were projected with a 35 mm projector (Vanguard Instrument Corp) on a ground glass screen The first completely opacified left ventricular beat (2 to 3 seconds after the onset of injection) was utilized to determine left ventricular volumes The area of the left ventricular cavity was obtained with an electronic digitizer (Graf/Pen, Science Accessories Corp) interfaced to a digital computer (Hewlett Packard) for calculating volumes The left ventricular end diastolic volume index and ejection fraction determined in 20 patients with normal left ventricles by this method was 69 ± 19 and 0 68 ± 0 10 ml per square meter, respectively The reproducibility of determining left ventricular volumes and ejection fractions on different opacified beats has been demonstrated by us[1] as well as by others All the patients with single vessel disease had a normal end diastolic volume in Study A and only one had an abnormally diminished ejection fraction (0 46) Only one patient with double vessel disease had an abnormal end diastolic volume (112 ml per square meter) and three had an abnormal ejection fraction (0 41, 0 46 and 0 47) three patients with triple vessel disease had an abnormal end diastolic volume (102 147 and 167 ml per square meter) and four had an abnormal ejection fraction (0 38 0 41 0 42 and 0 45) In each study, the per cent shortening of the major and minor axis from the end diastole to end systole was determined Ventriculograms were evaluated by the superimposition of the end diastolic and end systolic silhouette with the mid aortic valve and apex as fixed points Since two beats in the same patient were compared with each other no attempt was made to correct for rotation of the heart or downward displacement of the base One transverse minor axis was drawn which bisected at right angles the line defining the long major axis (mid aortic to apex) of the heart All results were expressed as the mean ± one standard deviation of the mean with comparison between Studies A and B and between groups determined with paired and unpaired Student s t tests respectively

Epicardial marker study Radiopaque markers are routinely placed adjacent to the proximal and distal anastomotic site at the time of aortocoronary bypass surgery In seven patients saphe

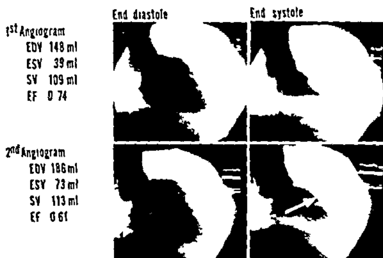


Fig 2 Duplicate angiographic study of a patient with single vessel disease of the left anterior descending artery Injection of contrast medium is made in the left ventricle via a retrograde catheter Note the changes in end diastolic volume end systolic volume and only a slight increase in the stroke volume The ejection fraction decreased in the second study Also note as shown by the arrow impaired movement of the anterior wall of the left ventricle during the second angiographic study which was not present in the first angiographic study

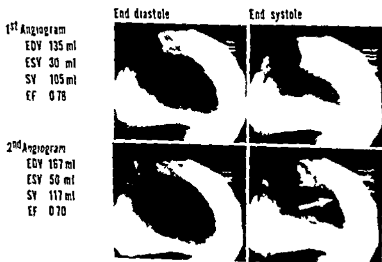


Fig 3 Duplicate angiographic study of a patient with double vessel disease (RCA and LAD) with injection of contrast medium into the left ventricle via a transseptal catheter Note changes in the heart volumes and ejection fraction. Observe as noted by the arrow the impaired movement of the anterior wall of the left ventricle which was not present in the first angiographic study

significant difference in systemic pressure or heart rate when Study B was compared to Study A (Table I) The normal group and the single vessel disease groups both demonstrated a significant increase ($p < 0.005$) in the stroke volume in Study B as compared to Study A whereas there was no significant change observed in either the double or triple vessel disease groups (Table I) In the latter two groups six patients revealed either no change or a decrease in stroke volume in Study B as compared to Study A

In no patient in the normal group was there any striking difference in the left ventricular contractile pattern when Study B was compared to Study A (Fig 1) whereas two of the 10 patients in the single vessel disease group demonstrated impaired localized left ventricular contractile pattern in the second angiogram which was not

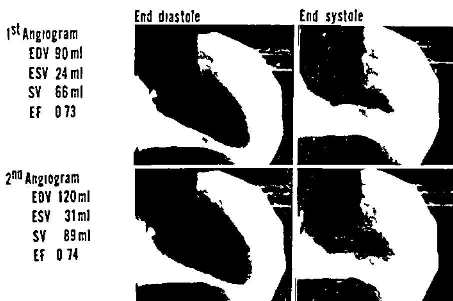


Fig 1 Duplicate angiographic study of a patient with no evidence of cardiac disease. The injection of the contrast medium is made in the left atrium via a transseptal catheter. The second angiogram was performed 3 minutes after the first angiogram. Note in the second angiogram an increase in both the end diastolic volume and stroke volume with no change in the ejection fraction.

Table II Left ventricular end diastolic volume and pressure changes during angiographic study*

	Change in end diastolic volume (ΔV)		**Change in end-diastolic pressure (ΔP) (mm Hg)*	*ΔV/ΔP*	
	ml	*ml/M*		*ml/mm Hg*	*ml/M /mm Hg*
Normal group	25.5 ± 12.8	13.8 ± 6.0	4.5 ± 1.6	6.0 ± 2.4	3.3 ± 1.1
Arteriosclerotic group					
Single vessel disease	26.1 ± 9.2	13.7 ± 5.3	7.3 ± 3.6	5.0 ± 3.8	2.6 ± 2.2
Double vessel disease	24.8 ± 11.4	12.5 ± 6.3	12.1 ± 4.5†	2.3 ± 1.4‡	1.1 ± 0.7‡
Triple vessel disease	26.8 ± 13.6	15.5 ± 7.3	12.0 ± 5.1†	2.7 ± 1.7‡	1.5 ± 1.0‡

Changes noted are the differences observed between Studies A and B (see Table I). Figures represent mean and ±1 standard deviation.
†When compared to either the normal group or the single vessel disease group the significance was $p < 0.01$
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performed 3 minutes later (Study B) are shown in Table I. In all the groups studied the ejection fraction and heart rate were not significantly different when Studies A and B were compared. In no patient in the normal group was there a decrease or more than a slight increase (< 10 per cent) in the ejection fraction in Study B as compared to Study A, whereas in the single vessel disease group one patient had a 13 per cent decrease and another patient had an 11 per cent increase in the ejection fraction observed on the second angiographic study. Five of the 24 patients with double or triple vessel disease demonstrated a greater than 10 per cent decrease in the ejection fraction, whereas three had a greater than 10 per cent increase in ejection fraction in Study B when compared to Study A. In all the groups evaluated there was a significant increase ($p < 0.005$) in both the left ventricular end diastolic volume and end diastolic pressure in the second angiographic study. The increase in the end diastolic volume (ΔV) in all the groups studied revealed no significant difference when they were compared with each other (Table II). However, the increase observed in end diastolic pressure in the double and triple vessel disease group was significantly greater ($p < 0.01$) when compared to both the normal and single vessel disease group (Table II). Thus as a result of equivalent volume changes (ΔV) in all the groups studied but differences in pressure change (ΔP), the ratio of ΔV/ΔP was significantly lower ($p < 0.001$) in the double or triple vessel disease group than either the normal or the single vessel disease group. There was no

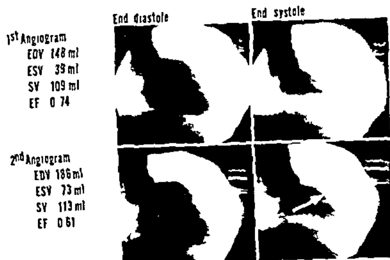


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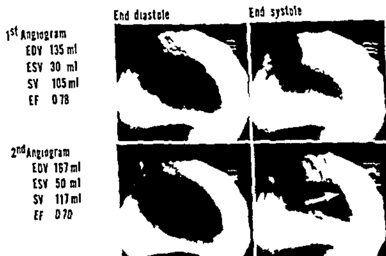


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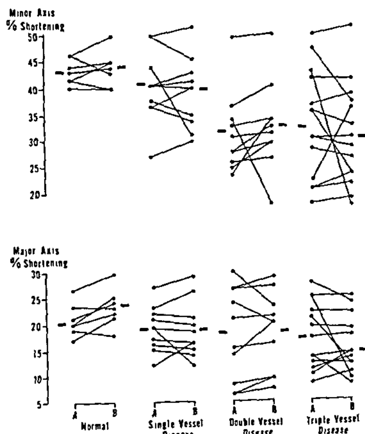


Fig 4 The per cent shortening of the minor and major axes for individual patients for the groups studied The horizontal bar represents the mean for Studies A and B for each group

present during the first angiographic study (Fig 2) In seven of the 24 patients with double or triple vessel disease the second angiographic study demonstrated either further deterioration of an area previously demonstrating asynergy or impaired contractile pattern not present in the first study (Fig 3) Two patients demonstrated an improved left ventricular contractile pattern on the second angiographic study when compared to the first study In all the patients showing a change in the contractile pattern on the second angiography study, significant coronary artery disease was present in the vessel supplying the involved myocardial segment Quantitative evaluation of the contractile pattern on the basis of per cent shortening of the major and minor axis of the left ventricle at end systolic revealed for all the groups studied no significant differences when the mean values of Study A were compared to Study B (Fig 4) However individual changes were apparent in the groups with arteriosclerotic heart disease which were not observed in the normal group In the normal group both the major and minor axis demonstrated little or no change in per cent of shortening in Study B as compared to Study A (Fig 4) In one patient having single vessel disease there was an appreciable decrease in per cent of shortening of both the major and minor axis in Study B as compared to Study A (Figs 2 and 4) In the patients with double or triple vessel disease, as noted in Fig 4, the response to the second angiogram was variable, with three demonstrating a large decrease in the per cent shortening of the minor axis and six patients revealing a significant decrease in the per cent shortening of the major axis Three patients revealed an appreciable increase in the per cent of shortening of one of the axes (Fig 4)

Epicardial marker study In Fig 5 is an example of the frame by frame distance between two epicardial markers (clips) for one cardiac cycle before and at various time intervals after the left ventricular angiogram In this patient, as in all the patients undergoing cinegraphic clip studies the heart rate was kept constant with a temporary transvenous pacemaker in the right atrium Fig 6 shows for all seven patients who had cinefluorographic epicardial clip studies the mean per cent change (± S E M) in intraclip distance at end diastolic as compared to the preangiographic intraclip distance The same figure displays the mean (± S E M) left ventricular end diastolic pressure obtained at the time of each cinegraphic study It is evident in both Figs 5 and 6 that the end diastolic intraclip distance increased after the left ventricular angiogram with the maximum increase occurring between 1 and 3 minutes after the left ventricular angiogram Fifteen minutes after the left ventricular angiogram the intraclip distance had not returned to values obtained prior to the left ventricular angiogram (Fig 6) Furthermore as shown in Fig 6 the change in the intraclip distance correspond to the change noted in the left ventricular end diastolic pressure

Discussion

The present study demonstrates that the injection of radiographic contrast medium during angiographic studies is accompanied by an increase in the left ventricular end diastolic volume Furthermore as indicated by the cinegraphic clip studies (Figs 5 and 6) such changes in the end diastolic volume last over 15 minutes Thus it is readily apparent that any sequential angiographic study in man should be performed at not less than 15 minute intervals It is well

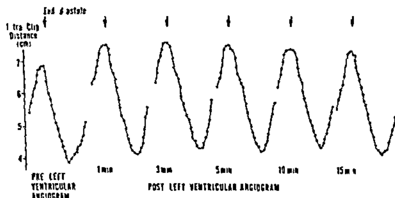


Fig 5 Frame by frame plot of the distance between two epicardial markers (clips) for one cardiac cycle before and after a left ventricular angiogram The arrows indicate end-diastole Heart rate kept constant throughout study with atrial pacing Note initial increase after the angiogram of the intraclip distance which gradually decreases after the third minute but does not return to the preangiogram distance at 15 minutes

appreciated that after the injection of angiographic contrast medium there is an increase in plasma osmolality which is accompanied by an increase in intravascular volume [11] The magnitude of the increase in intravascular volume ranges from 2 7 to 27 per cent [3] The maximum increase in blood volume occurs between 1 and 2 minutes after the injection of the contrast medium and is directly related to the amount of contrast medium injected [6] The fall in hematocrit and serum chloride associated with the increase in blood volume is consistent with the transfer of water from the cellular compartment into the intravascular space Iseri and associates noted that the increase in plasma volume may last up to 15 minutes The time sequence observed in changes in the intravascular volume[6] corresponded to the present cinegraphic clip study of altered end diastolic clip measurements whereby the maximum increase in intraclip distance occurred between 1 and 3 minutes after the left ventricular angiogram and lasted up to 15 minutes

The changes noted in the seven patients having no evidence of organic heart disease which included a significant increase in left ventricular end diastolic pressure end diastolic volume and stroke volume accompanied by little or no increase in end systolic volume ejection fraction and per cent shortening of the major and minor axes are also similar to that observed in the dog after acute expansion of the blood volume by dextran infusion [21] The patients with coronary artery disease behaved somewhat differently from the patients with normal left ventricles Although

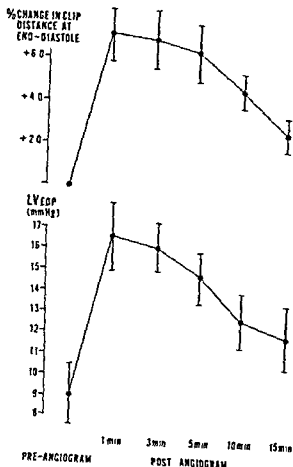


Fig 6 The per cent shortening of the intraclip distance at end-diastole (upper) and the corresponding left ventricular end-diastolic pressure (LV$_{EDP}$) before and after left ventricular angiography Each point represents the mean (± 1 S.E M) for the seven patients studied. Note that the change in intraclip distance corresponds to the change in the end-diastolic pressure Also note that these values have not returned to the preangiographic levels even 15 minutes after the angiogram

all the patients demonstrated a significant increase in the left ventricular end diastolic pressure after the first angiographic study, the magnitude of the increase was significantly greater in the groups with double- or triple-vessel disease as compared to both the normal group and the single-vessel disease group (Table II). These findings are similar to those reported by Brundage and Cheitlin.[1] However, in the present study, in spite of the significant differences in the response of the end diastolic pressure between the groups studied, there was no difference in the incremental change in end diastolic volume. Thus the change in volume per unit pressure change ($\Delta V/\Delta P$ in Table II) was significantly less in patients with double- and triple-vessel disease as compared to both the group with normal left ventricle and the group with single-vessel disease. This does not necessarily indicate that the patients with double- and triple-vessel disease have a diminished compliance but may rather indicate that these patients are operating on a steeper portion of the pressure volume curve as compared to the groups with normal left ventricle and single-vessel disease.

In the seven patients undergoing cinefluorographic clip studies, the changes in intraclip distance corresponded to the changes observed in the left ventricular end diastolic pressure. Thus it can be concluded that in these seven patients, none of whom had a prior myocardial infarction or abnormal left ventricular function, the end diastolic pressure reflected a change in size of the heart. This agrees with the observation by Mullins and co-workers[11] in dogs that the increased end diastolic pressure associated with injection of contrast medium followed the same pattern as that of the end diastolic volume. Therefore, both the angiographic and epicardial clip study demonstrate that the increase in left ventricular end diastolic pressure associated with the injection of angiographic contrast media may in part be explained by an increase in the end diastolic volume secondary to an acute increase in the intravascular volume.

Interpretation of the changes in end diastolic pressure after angiographic studies to evaluate left ventricular function has certain limitations. It is uncertain whether contrast media may not directly alter left ventricular compliance. Prior studies in both dog and man[1-4] have indicated that the injection of angiographic contrast medium is associated with depressed myocardial contractility which may start after the fourth or fifth opacified beat and last up to 15 minutes. These studies, as well as others,[3] indicate that physiologic information derived only from the first two or three opacified ventricular beats is valid for clinical and investigative data. The present study was not designed to evaluate the effect of angiographic contrast medium on left ventricular contractility. The 3 minute interval between the duplicate angiographic study was intentionally chosen since prior studies[11-13,16] as well as the epicardial clip study (Fig. 6) indicate that the maximum increase in the left ventricular end diastolic pressure noted after an angiogram occurs 2 to 4 minutes after the injection of contrast medium. However, an evaluation of the contractile pattern 3 minutes after the first angiographic study revealed differences in response of normal left ventricles as compared to those involved with arteriosclerotic heart disease. In the normal group, in spite of a significant increase in end diastolic volume 3 minutes after the first angiographic study, there was little if any change in ejection fraction and no significant change in end systolic volume. This resulted in an increased stroke volume of the same order of magnitude as that of the increase in end diastolic volume. The left ventricular contractile pattern remained unchanged (Fig. 1). With but two exceptions, the group with single-vessel disease responded in a similar manner. One patient with single-vessel disease demonstrated on the second angiographic study a decrease in ejection fraction (0.74 to 0.61) due to only a slight increase in the stroke volume and an increase in end systolic volume accompanied by impairment in contractile pattern not previously present (Fig. 2). A second patient with single-vessel disease revealed an increase in the ejection fraction (0.56 to 0.65) associated with a decrease in the end systolic volume accompanied by improved shortening of the major axis and contractile pattern. In the patients with double- or triple-vessel disease, the response 3 minutes after the initial angiographic study indicated depression of myocardial contractile pattern in some and improvement in others. It would be difficult to explain localized abnormalities of contraction as noted in some patients on the second angiographic study (Figs. 2 and 3) as due to the direct depressant effect of the contrast medium. A major determinant of myocardial

oxygen consumption is intramyocardial tension which is determined by both ventricular pressure and volume Therefore it can be anticipated that after the first angiographic study which was accompanied by an increase in both the end diastolic pressure and volume the myocardial oxygen consumption was increased It should be noted that the areas of the left ventricle that demonstrated deterioration of contraction were supplied by diseased coronary arteries Thus it may be speculated that marginal coronary blood flow was further compromised by an increased oxygen demand resulting in localized ischemia This may explain why in our experience an occasional patient with arteriosclerotic heart disease may experience angina pectoris after a left ventricular angiogram An explanation for an improved contractile pattern noted in some patients is not readily apparent

Summary

Forty one patients had left ventricular angiography repeated 3 minutes after an initial study in order to evaluate the effect of angiographic contrast medium on left ventricular end diastolic pressure (EDP) and volume (EDV) Seven patients had no evidence of heart disease (normal group) and 34 patients had coronary artery disease Single vessel disease was present in 10 double vessel disease in 10 and triple vessel disease in 14 patients Seven other patients with radiopaque epicardial clips previously attached to the left ventricle underwent cinefluorographic studies to determine end diastolic intraclip distance at various intervals after a left ventricular angiogram

In all the groups studied there was a significant increase ($p < 0\,005$) in both the left ventricular EDP and EDV in the second angiographic study as compared to the first This increase in EDV (ΔV) was similar in all groups However the increase in EDP (ΔP) was significantly greater ($p < 0\,01$) in patients with double and triple vessel disease as compared to the normal and single vessel disease groups Ejection fraction per cent shortening of the heart axis and contractile pattern in the normal subjects were not significantly different when the second angiographic study was compared to the first In nine of 34 patients with coronary artery disease the second angiographic study demonstrated impairment in left ventricular contractile pattern not present in the first angiographic study Cinefluorographic study demonstrated an increase in end diastolic intraclip distance after the left ventricular angiogram The change in intraclip distance corresponded directionally and temporally to the changes in left ventricular EDP The present study revealed that the increase in left ventricular end diastolic pressure associated with the injection of angiographic contrast medium can be explained by an increase in EDV and that such changes last for over 15 minutes and may be associated with alterations in the contractile pattern of the left ventricle

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REFERENCES

1 Karliner J S., Bouchard R J., and Gault J H Haemodynamic effects of angiographic contrast material in man A beat by beat analysis Br Heart J 34 347 1972
2 Carleton R A Change in left ventricular volume during angiocardiography Am J Cardiol 27 460 1971
3 Hammermeister K. E and Warbasse J R Immediate hemodynamic effects of cardiac angiography in man Am J Cardiol. 31 307 1973
4 Zelis R Mason D T Spann, J F., Jr., and Amsterdam E A Alterations of cardiac contractility and peripheral circulatory dynamics produced by angiographic dye in man (abst) Clin Res 18 118 1970
5 Giammona S T., Lurie P R., and Segar W E. Hypertonicity following selective angiocardiography Circulation 28 1096 1963
6 Isen, L. T Kaplan M A Evans M J and Nickel, E D Effect of concentrated contrast media during angiography on plasma volume and plasma osmolality Am Heart J 69 154 1965
7 Gootman N Rudolph A M and Buckley N M Effect of angiographic contrast media on cardiac function Am J Cardiol. 25 59 1970
8 Carleton R A., and Clark J G Left ventricular function during angiocardiography Am J Med Sci. 257 81 1969
9 Behar V S Waxman M B and Morris J J., Jr Effects of contrast medium (sodium iothalamate 80%) on left ventricular function Am J Med Sci. 260 202 1970
10 Mullins C B Leshin S J Mierzwiak D S., Alsobrook H D and Mitchell, J H Changes in left ventricular function produced by the injection of contrast media Am Heart J 83 373 1972
11 Rahimtoola S H., Duffy J P and Swan H J C Hemodynamic changes associated with injection of angiocardiographic contrast medium in assessment of valvular lesions Circulation 33 52 1966
12 Cohn P F., Horn H R., Teichholz L. E Kreulen T H., Herman M V and Gorlin R Effects of angiographic contrast medium on left ventricular function in coronary artery disease Am J Cardiol. 32 21 1973
13 Brown R., Rahimtoola S H David G D and Swan H J C The effect of angiocardiographic contrast

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Summary

Forty one patients had left ventricular angiography repeated 3 minutes after an initial study in order to evaluate the effect of angiographic contrast medium on left ventricular end diastolic pressure (EDP) and volume (EDV). Seven patients had no evidence of heart disease (normal group) and 34 patients had coronary artery disease. Single vessel disease was present in 10, double vessel disease in 10, and triple vessel disease in 14 patients. Seven other patients with radiopaque epicardial clips previously attached to the left ventricle underwent cinefluorographic studies to determine end diastolic intraclip distance at various intervals after a left ventricular angiogram.

In all the groups studied there was a significant increase ($p < 0.005$) in both the left ventricular EDP and EDV in the second angiographic study as compared to the first. This increase in EDV (ΔV) was similar in all groups. However, the increase in EDP (ΔP) was significantly greater ($p < 0.01$) in patients with double and triple vessel disease as compared to the normal and single vessel disease groups. Ejection fraction, per cent shortening of the heart axis, and contractile pattern in the normal subjects were not significantly different when the second angiographic study was compared to the first. In nine of 34 patients with coronary artery disease the second angiographic study demonstrated impairment in left ventricular contractile pattern not present in the first angiographic study. Cinefluorographic study demonstrated an increase in end-diastolic intraclip distance after the left ventricular angiogram. The change in intraclip distance corresponded directionally and temporally to the changes in left ventricular EDP. The present study revealed that the increase in left ventricular end diastolic pressure associated with the injection of angiographic contrast medium can be explained by an increase in EDV and that such changes last for over 15 minutes and may be associated with alterations in the contractile pattern of the left ventricle.

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REFERENCES

1. Karliner, J. S., Bouchard, R. J., and Gault, J. H.: Haemodynamic effects of angiographic contrast material in man. A beat by beat analysis, Br. Heart J. 34:347, 1972.
2. Carleton, R. A.: Change in left ventricular volume during angiocardiography, Am. J. Cardiol. 27:460, 1971.
3. Hammermeister, K. E., and Warbasse, J. R.: Immediate hemodynamic effects of cardiac angiography in man, Am. J. Cardiol. 31:307, 1973.
4. Zelis, R., Mason, D. T., Spann, J. F., Jr., and Amsterdam, E. A.: Alterations of cardiac contractility and peripheral circulatory dynamics produced by angiographic dye in man (abst.), Clin. Res. 18:118, 1970.
5. Giammona, S. T., Lurie, P. R., and Segar, W. E.: Hypertonicity following selective angiocardiography, Circulation 28:1096, 1963.
6. Isen, L. T., Kaplan, M. A., Evans, M. J., and Nickel, E. D.: Effect of concentrated contrast media during angiography on plasma volume and plasma osmolality, AM. HEART J. 69:154, 1965.
7. Gootman, N., Rudolph, A. M., and Buckley, N. M.: Effect of angiographic contrast media on cardiac function, Am. J. Cardiol. 25:59, 1970.
8. Carleton, R. A., and Clark, J. G.: Left ventricular function during angiocardiography, Am. J. Med. Sci. 257:81, 1969.
9. Behar, V. S., Waxman, M. B., and Morris, J. J., Jr.: Effects of contrast medium (sodium iothalamate 80%) on left ventricular function, Am. J. Med. Sci. 260:202, 1970.
10. Mullins, C. B., Lesbin, S. J., Mierzwiak, D. S., Alsobrook, H. D., and Mitchell, J. H.: Changes in left ventricular function produced by the injection of contrast media, AM. HEART J. 83:373, 1972.
11. Rahimtoola, S. H., Duffy, J. P., and Swan, H. J. C.: Hemodynamic changes associated with injection of angiocardiographic contrast medium in assessment of valvular lesions, Circulation 33:52, 1966.
12. Cohn, P. F., Horn, H. R., Teichholz, L. E., Kreulen, T. H., Herman, M. V., and Gorlin, R.: Effects of angiographic contrast medium on left ventricular function in coronary artery disease, Am. J. Cardiol. 32:21, 1973.
13. Brown, R., Rahimtoola, S. H., David, G. D., and Swan, H. J. C.: The effect of angiocardiographic contrast

all the patients demonstrated a significant increase in the left ventricular end diastolic pressure after the first angiographic study, the magnitude of the increase was significantly greater in the groups with double or triple vessel disease as compared to both the normal group and the single vessel disease group (Table II) These findings are similar to those reported by Brundage and Cheitlin[1] However in the present study, in spite of the significant differences in the response of the end diastolic pressure between the groups studied there was no difference in the incremental change in end diastolic volume Thus the change in volume per unit pressure change ($\Delta V/\Delta P$ in Table II) was significantly less in patients with double and triple vessel disease as compared to both the group with normal left ventricle and the group with single vessel disease This does not necessarily indicate that the patients with double and triple vessel disease have a diminished compliance but may rather indicate that these patients are operating on a steeper portion of the pressure volume curve as compared to the groups with normal left ventricle and single vessel disease

In the seven patients undergoing cinefluorographic clip studies the changes in intraclip distance corresponded to the changes observed in the left ventricular end diastolic pressure Thus it can be concluded that in these seven patients none of whom had a prior myocardial infarction or abnormal left ventricular function the end diastolic pressure reflected a change in size of the heart This agrees with the observation by Mullins and co workers[11] in dogs that the increased end diastolic pressure associated with injection of contrast medium followed the same pattern as that of the end diastolic volume Therefore both the angiographic and epicardial clip study demonstrate that the increase in left ventricular end diastolic pressure associated with the injection of angiographic contrast media may in part be explained by an increase in the end diastolic volume secondary to an acute increase in the intravascular volume

Interpretation of the changes in end diastolic pressure after angiographic studies to evaluate left ventricular function has certain limitations It is uncertain whether contrast media may not directly alter left ventricular compliance Prior studies in both dog and man[1, 4] have indicated that the injection of angiographic contrast medium is associated with depressed myocardial contractility which may start after the fourth or fifth opacified beat and last up to 15 minutes These studies as well as others [3] indicate that physiologic information derived only from the first two or three opacified ventricular beats is valid for clinical and investigative data The present study was not designed to evaluate the effect of angiographic contrast medium on left ventricular contractility The 3 minute interval between the duplicate angiographic study was intentionally chosen since prior studies[11, 13, 16] as well as the epicardial clip study (Fig 6) indicate that the maximum increase in the left ventricular end diastolic pressure noted after an angiogram occurs 2 to 4 minutes after the injection of contrast medium However an evaluation of the contractile pattern 3 minutes after the first angiographic study revealed differences in response of normal left ventricles as compared to those involved with arteriosclerotic heart disease In the normal group in spite of a significant increase in end diastolic volume 3 minutes after the first angiographic study there was little if any change in ejection fraction and no significant change in end systolic volume This resulted in an increased stroke volume of the same order of magnitude as that of the increase in end diastolic volume The left ventricular contractile pattern remained unchanged (Fig 1) With but two exceptions the group with single vessel disease responded in a similar manner One patient with single vessel disease demonstrated on the second angiographic study a decrease in ejection fraction (0 74 to 0 61) due to only a slight increase in the stroke volume and an increase in end systolic volume accompanied by impairment in contractile pattern not previously present (Fig 2) A second patient with single vessel disease revealed an increase in the ejection fraction (0 56 to 0 65) associated with a decrease in the end systolic volume accompanied by improved shortening of the major axis and contractile pattern In the patients with double or triple vessel disease the response 3 minutes after the initial angiographic study indicated depression of myocardial contractile pattern in some and improvement in others It would be difficult to explain localized abnormalities of contraction as noted in some patients on the second angiographic study (Figs 2 and 3) as due to the direct depressant effect of the contrast medium A major determinant of myocardial

Familial occurrence of sinus bradycardia short PR interval intraventricular conduction defects recurrent supraventricular tachycardia, and cardiomegaly*

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The familial occurrence of cardiac disease has been reported with increasing frequency within the past decade Familial cardiomyopathy with or without outflow tract obstruction has been the subject of numerous reports [1] Similarly disorders of impulse formation and dysfunction of virtually every element of the cardiac conduction system have been linked to genetic defects trans mitted as an autosomal dominant trait with varying expressivity [4] [5] Hereditary Wolff Parkin son White (WPW) syndromes occurring with or without myocardial disease have also appeared sporadically in the literature [16] [2]

This study describes the clinical and electro physiologic findings in four members of a family presenting with sinus bradycardia a short PR interval intraventricular conduction defects recurrent supraventricular tachycardia (SVT) syncope and cardiomegaly Two members went on to develop third degree heart block requiring permanent pacemaker implantation The loca tion and place of residence of this family s rela tives was largely unknown precluding systematic study of the family pedigree The constellation of findings presented by the mother of this family and her three children is unusual and has not to our knowledge been previously reported

Clinical summary

Case 1 The mother (M A) was a 46-year old white woman with a 15 year history of recurrent arrhythmias Of interest she was one of 11 children eight of whom died from unknown causes their ages at death ranged from a few weeks to 7 years One brother 37 years of age required implantation of a permanent pacemaker because of a history of syncopal episodes with intermittent third-degree heart block progress ing to sustained complete heart block. Her father who had no heart disease died of carcinoma of the lung her mother died with an enlarged heart The mother had 10 siblings One had recurrent tachycardia and "most of the others" died of heart dropsy " There was no evidence of consanguinity in her immediate ancestors.

On Sept. 28 1970 the patient was brought to a local emergency room because of acute shortness of breath and severe anterior chest pain An electrocardiogram (ECG) revealed probable atrial fibrillation with an irregular ventric ular rate up to 220 beats per minute (Fig 1 *A*) Intravenous lidocaine administered because the ECG was interpreted as ventricular tachycardia resulted in prompt reversion to sinus rhythm. On Dec 8 1970 she developed syncope secondary to third-degree heart block with idioventricular rates of 24 beats per minute (Fig 1 *B*) A temporary transvenous pacemaker was positioned in the right ventricle via the right basilic vein following which the patient resumed sinus rhythm and was transferred to our hospital.

The blood pressure was 100/60 mm Hg and the pulse was 56 beats per minute and irregular Examination of the heart and lungs was unremarkable There were no murmurs gallops or signs of congestive heart failure Roentgenograms of the chest revealed mild cardiomegaly with a cardiothoracic ratio of 0.52. The ECG revealed sinus bradycardia with atrial premature beats. The PR interval was 110 msec The QRS duration was 120 msec., with a configuration of left bundle branch block (LBBB) (Fig. 2) A vectorcardiogram displayed none of the features of WPW syndrome but was typical of LBBB His

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medium on circulatory dynamics in man Cardiac output during angiocardiography Circulation **31** 234 1965
14 Brown A K Epstein E J Coulshed N Clarke J M and Doukas N G Haemodynamic changes after angio cardiography Br Heart J **31** 233 1969
15 Rahimtoola S H Duffy J P and Swan H J C Ventricular performance after angiocardiography Circu lation **35** 70 1967
16 Brundage B H and Cheitlin M D Left ventricular angiography as a function test Chest **64** 70 1973
17 Brundage B H and Cheitlin M D Ventricular func tion curves from the cardiac response to angiographic contrast A sensitive detector of ventricular dysfunction in coronary artery disease AM HEART J **88** **281** 1974
18 Proudfit W L Shirey E K Sheldon W C and Sones F M Jr Certain clinical characteristics correlated with extent of obstructive lesions demonstrated by selective cinecoronary arteriography Circulation **38** 947 1968
19 Dodge H T Sandler H Ballew D W and Lord J D The use of biplane angiocardiography for measurement of left ventricular volume in man AM HEART J **60** 762 1960
20 Kasser I S and Kennedy J W Measurement of left ventricular volumes in man by single plane cineangiocar diography Invest Radiol **4** 83 1969
21 Hamby R I Aintablian A Wisoff B G and Hart stein M L *Response of the left ventricle to postextra* systolic potentiation Prediction of post operative ven tricular function in coronary artery disease Circulation **51** 428 1975
22 Cohn P F Levine J A Bergerson G A and Gorlin R Reproducibility of the angiographic left ventricular ejection fraction in patients with coronary artery disease AM HEART J **88** 713 1974
23 Harrison D C Goldblatt A and Braunwald E Studies on cardiac dimensions in intact unanesthetized man I Description of techniques and their validation Circ Res **13** 448 1963
24 Meckstroth C V and Cattaneo S M Juxtaposed epicardial pericardial clips An adjunct to the differential diagnosis of hemopericardium pericardial tamponade and primary low cardiac output syndrome after open heart surgery J Thorac Cardiovasc Surg **68** 447 1975
25 Liedtke A J Pasternac A Sonnenblick E H and Gorlin R Changes in canine ventricular dimensions with acute changes in preload and afterload Am J Physiol **234** 820 1972
26 Sonnenblick E H Ross J Jr and Braunwald E Oxygen consumption of the heart Newer concepts of its multifactoral determination Am J Cardiol **22** 328 1968

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Clinical summary

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The blood pressure was 100/60 mm Hg and the pulse was 56 beats per minute and irregular Examination of the heart and lungs was unremarkable There were no murmurs gallops or signs of congestive heart failure Roentgenograms of the chest revealed mild cardiomegaly with a cardiothoracic ratio of 0.52 The ECG revealed sinus bradycardia with atrial premature beats. The PR interval was 110 msec The QRS duration was 1 0 msec with a configuration of left bundle branch block (LBBB) (Fig 2) A vectorcardiogram displayed none of the features of WPW syndrome but was typical of LBBB His

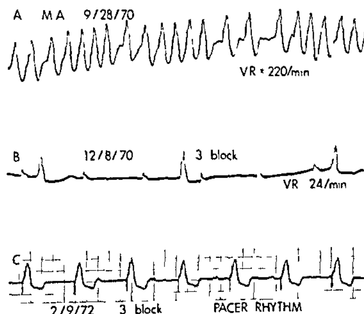


Fig 1 Monitoring ECG strips on Patient M A demonstrating atrial fibrillation with rapid ventricular response (Panel *A*) third degree heart block (*B*) and permanent pacer rhythm in presence of third degree block (*C*) *A* and *B* were retouched for clarity

bundle studies were performed and will be described separately

The patient then had implantation of a permanent demand pacemaker and was maintained on digoxin and procainamide An ECG taken Feb 9 1972 revealed sinus rhythm with complete heart block and a permanent pacer rhythm (Fig 1 C) The patient had become completely dependent on her pacemaker

Case 2 The patient (M G) the 24 year old daughter of M A also had a history of frequent palpitations and recurrent SVT for several years The tachycardias were accompanied by a feeling of weakness and faintness but not syncope She had never experienced any overt signs or symptoms of congestive heart failure On physical examination the blood pressure was 120/70 mm Hg and the pulse ranged from 44 to 70 beats per minute with some irregularity The heart was markedly enlarged to the left Heart sounds were of normal quality with no gallops clicks snaps or rubs being present A harsh Grade 2/6 ejection murmur was heard along the left sternal border with no radiation to the carotid vessels There was no hepatomegaly and no peripheral edema

Roentgenograms of the chest revealed marked enlargement of the left ventricle with clear peripheral lung fields (Fig 3) The ECG (Fig 4) revealed sinus rhythm with a mean electrical axis of minus 10 degrees and a PR interval of 90 msec. Generalized intraventricular conduction defects were present with a QRS duration of 120 msec The voltage in Leads I aV_L and V to V was markedly increased and probably reflected left ventricular hypertrophy There was marked T wave inversion in these same leads A vectorcardiogram ruled out the presence of a WPW syndrome

Right and left heart catheterization and angiography performed on March 23 1972 revealed severe left ventricular hypertrophy with no evidence of right or left ventricular outflow obstruction (Fig 3) There was no evidence of valvular disease and both left and right coronary arteries were large and free of occlusive disease His bundle studies were performed and will be described separately Two months after this study the patient developed syncope with complete heart block requiring insertion of a permanent pacemaker Since then she has had no syncopal episodes

Case 3 The oldest son (K A) was studied because of sinus bradycardia palpitations, recurrent SVT and several episodes of syncope The patient was anxious to have this study because an apparently healthy 16 year old maternal cousin had been found dead in bed the week before K A was a 19 year-old boy who had experienced two syncopal episodes while at rest in the year prior to admission He was told by his physician that he had very slow heart rates at that time He had no other cardiovascular symptoms.

The blood pressure was 110/80 mm Hg and the pulse was 56 beats per minute and regular The remainder of his physical examination was within normal limits The chest x ray revealed mild cardiomegaly with a cardiothoracic ratio of 0 52 The ECG revealed sinus bradycardia a PR interval of 80 msec and a QRS duration of 110 msec The mean electrical axis was minus 30 degrees with a T wave vector of plus 75 degrees The R wave in V_5 was 35 mm The QT interval was normal Right and left heart catheterization performed on July 14 1972 revealed normal resting hemodynamics with mild left ventricular hypertrophy The left and right coronary arteries were entirely normal throughout their entire course His bundle studies were performed A permanent demand pacemaker was implanted on July 19 1972 following which he has had no further syncopal episodes.

Case 4 T A was the 16 year old son who also had bradycardia with occasional bouts of SVT His physician had noted rates of 40 beats per minute associated with dizziness and near syncope He had no other signs or symptoms referable to the cardiovascular system

The blood pressure was 110/70 mm Hg and the pulse was 50 beats per minute and regular There were no other abnormal physical findings Roentgenograms of the chest revealed mild left ventricular enlargement The ECG revealed sinus bradycardia at a rate of 52 beats per minute with a normal electrical axis. The PR interval was 120 msec and the QRS was 100 msec in duration Voltage criteria for left ventricular hypertrophy were present but the ST T wave vectors were normal His bundle recordings will be described in the next section A permanent pacemaker was suggested but has not yet been implanted

Electrophysiologic studies

His bundle studies were performed by methods previously described by Scherlag and associates [1] Recordings of two standard ECG leads and intracardiac electrograms were displayed on a DR 12 Electronics for Medicine oscilloscope and recorded on photographic paper at speeds of 100 mm per second with time lines 1 second apart Frequencies between 40 and 500 Hz were selected for recording electrograms Mid right atrial pacing was performed at various rates with a bipolar pacing catheter and a Cordis Synchrocor II battery driven pacemaker which delivered

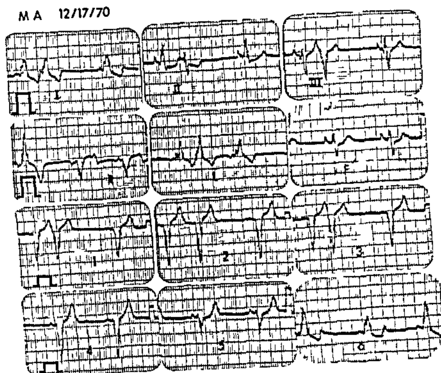


Fig 2 ECG of M. A., mother of the family

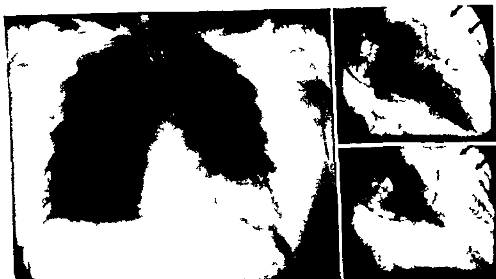
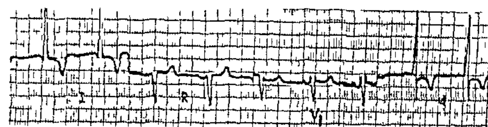


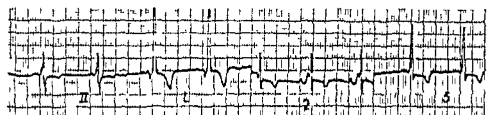
Fig 3 PA chest roentgenogram of M G Note cardiomegaly with marked left ventricular preponderance Upper right cine film of left ventricular angiogram RAO view end-diastole Lower right end-systole note massive LV thickening The arrows point to the outermost portions of the LV wall

impulses of 2 msec duration at twice threshold levels Resting PR interval was measured in the conventional scalar ECG leads during pacing the stimulus artifact was used to mark the beginning of low atrial depolarization seen in the His electrogram to the beginning of the His deflection Normal A H values in our lab in normal patients range from 60 to 130 msec The H V interval was taken from the beginning of the His deflection to the earliest onset of ventricular depolarization seen in any of the recorded leads Our normal values lie between 35-50 msec

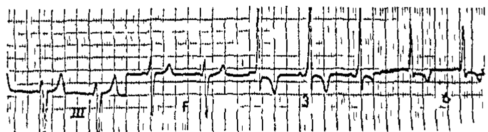
M G 3/22/72



1/2 Standard



1/2 Standard



1/2 Standard

Fig 4 ECG at half standard of M C

Table I A V conduction times during NSR and right atrial pacing*

Patient	*Rhythm*	*Rates (beats/min)*	*PR (msec)*	*A H (msec)*	*H V (msec)*	*AVB during atrial pacing*
M A 46 F	NSR	65	120	50	50	No
	RAP	116	150	50	50	No
	RAP	166	150	50	50	No
	RAP	180	150	50	50	No
	RAP	208	170	70	50	No
M G 24 F	NSR	80	105	30	40	No
	RAP	150	105	30	40	No
	RAP	180	118	30	48	No
	RAP	193	120	30	50	No
K A 19 M	NSR	60	110	55	35	No
	RAP	120	140	55	35	No
	RAP	160	150	60	35	No
	RAP	180	155	70	35	No
	RAP	215	180	95	35	2
T A 16 M	NSR	60	120	50	40	No
	RAP	130	140	65	40	No
	RAP	150	140	70	40	No
	RAP	170	180	80	40	No

Abbreviations
A H = interval from onset of low atrial depolarization to onset of His deflection
AVB = atrioventricular block
H V = interval from onset of His deflection to earliest onset of ventricular depolarization as measured from surface ECG leads or the ventricular electrogram
PR = interval from beginning of P wave to beginning of QRS as measured in surface ECG leads
RAP = right atrial pacing
NSR = normal sinus rhythm

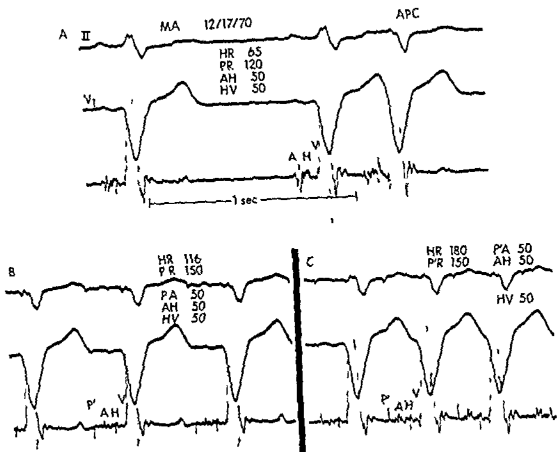


Fig 5 Case 1 In all panels ECG Lead II is followed by V, which is followed by HIS bundle electrogram (HBE) Time lines are at 1 second (*A*) The A H interval of 50 msec is short while H V is normal. With progressive increase in atrial pacing rates (*B*) and (*C*) A H and H V *remain unchanged APC* = *Atrial* premature contraction *HR* = heart rate *P A* = interval (in msec) from pacing stimulus artifact to onset of low atrial depolarization measured from HBE *P'R* = PR interval with pacing artifact marking beginning of P wave All other abbreviations are the same as those listed in Table I

Results

The electrophysiologic data are summarized in Table I

Case 1 The His bundle *electrograms in the* mother (M A) revealed a shortened A H interval and a high normal H V interval of 50 *msec Atrial* pacing even at rates of 180 beats *per minute* resulted in no change in the A H or H V intervals (Fig 5) The PR interval at rates of 180 per minute was still short at 150 msec *A minimal* increase in the A H interval occurred at pacing rates of 208 per minute Clearly there was *no* difficulty in transmitting atrial impulses *to the* ventricles Even at rates in excess of 180 per minute A V conduction proceeded on a 1 1 basis—an unexpected finding considering that one week previously she was in complete heart block.

Pacing at the His bundle site resulted in antegrade conduction to the ventricle and retrograde conduction to the atrium Of interest atrial depolarization appeared to have occurred in the high atrium first and 30 msec later in the low atrium suggesting that retrograde conduction bypassed the A V node perhaps through an anomalous bypass tract or the posterior intranodal tract reached the superior portion of the right atrium following which depolarization proceeded in a superior to inferior direction (Fig 6) The QRS duration decreased by 25 msec *suggesting* that the site of pacing was distal to an *area of* disease in *the* His bundle which was responsible for the marked widening of the resting QRS complex.

Case 2 Electrophysiologic studies reveal a short A H interval of 30 msec and a normal H V time of 40 msec During atrial pacing the A H interval remained constant *despite* atrial pacing

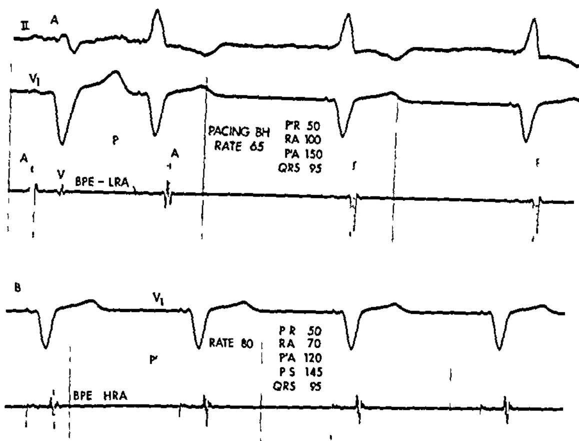


Fig 6 Case 1 Pacing bundle of HIS (BH) Bipolar electrogram is of the low right atrium (*BPE--LRA*) in Panel *A* and of the high right atrium (*BPE--HRA*) in Panel *B* Time lines are 1 second The P R in this instance is measured from the pacing impulse (*P*) to the onset of the R wave and equals 50 msec--the same as the H V interval Note that there is retrograde conduction to the atrium with earlier depolarization seen in the high right atrium The QRS duration is shorter with BH pacing (see text) Abbreviations as in Fig 5

at 193 per minute (Fig 7) At this rate the PR interval remained short at 120 msec the H V time increased slightly to 50 msec but A V conduction continued on a 1 1 basis At one point (Fig 8) atrial pacing at 96 per minute resulted in supraventricular tachycardia at a rate of 240 per minute This happened frequently during the procedure and was terminated either by continued atrial pacing or by mechanical stimulation of the atrium with the pacing catheter Note that the SVT occurred following a spontaneous atrial premature beat The next pacing stimulus occurred very early at 200 msec resulting in a markedly prolonged H V interval of 110 msec This delay in the His to Purkinje system was sufficient to set up a re entrant tachycardia

Case 3 His bundle studies on the older son (K A) revealed a short A H and a normal H V interval at all pacing rates including a maximum of 215 per minute (Fig 9) At this point, occasional blocked beats were noted proximal to the bundle of His The A H interval increased slightly as the pacing rate increased Nevertheless even at rates of 215 per minute, it remained well within the normal resting limits as did the PR interval which measured 180 msec at this rate

Case 4 The younger son (T A) had a normal H V interval which remained so at rapid atrial pacing rates (Fig 10) The A H interval was at the lower limits of normal and increased slightly with progressive increase in pacing rates Even at rates exceeding 170 per minute there was a 1 1 A V conduction and the PR interval remained short That anomalous A V nodal bypass tracts exist and are utilized in an antegrade and retrograde fashion is suggested by Fig 11 which shows spontaneous ventricular premature contractions (VPC) associated with a markedly shortened ventricular atrial conduction time of 110 msec

Table I summarizes the conduction characteristics observed in this family The A H interval was short while the H V time was normal in all patients The A H interval in the mother and daughter remained essentially unchanged despite rapid atrial pacing The A H intervals in the two boys increased but only minimally during rapid atrial pacing K A s A H interval increased only 40 msec while going from a resting rate of 60 per

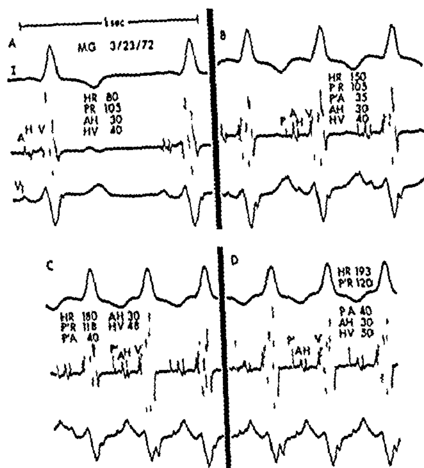


Fig. 7. Case ___. HBE between Leads I and V in all panels. The A-H interval is short (30 msec.) and remains unchanged with increasing atrial pacing rate. At rates of 180 and 193 per minute the H-V increases to 48 and 50 msec., respectively (Panels C and D). Abbreviations as in Fig. 5.

minute to a paced rate of 215 per minute and the A-H increased 30 msec. when his paced rate reached 170 per minute. The H-V interval increased slightly in M. G. with atrial pacing but remained within normal limits. In the other three members of the family it remained unchanged.

Discussion

ECG abnormalities are common accompaniments of familial myocardial disease. The abnormalities range from right bundle branch block (RBBB), LBBB, and diffuse intraventricular conduction defects to first-, second-, and third-degree heart block, to patterns of myocardial infarction, to atrial, ventricular, and junctional arrhythmias. The familial occurrence of conduction system disturbances unrelated to other familial cardiac disorders is being recognized with greater frequency. The conduction disturbances are at times quite specific for a given family and include involvement of the sinus node, the A-V node, the bundle of HIS, and the bundle branches. Prior to the pacemaker era, these afflicted patients would progress to complete heart block and an early death.

In 1952 Lown, Ganong, and Levine described the syndrome of short PR interval, normal QRS complex, and paroxysmal SVT. Thus far, this syndrome has not been linked to a genetic defect. Our patients did not have a normal QRS complex but the widened QRS was not related to a WPW syndrome. Vector studies did not demonstrate selective slowing of the initial QRS vector and electrophysiologic combined with pacing studies ruled out functioning Kent bundles or Mahaim fibers. Consequently, we believe they represent examples of the L-G-L syndrome.

Although the mechanism producing these findings had been unclear and the cause of SVT unknown, recent studies of A-V conduction in man with His bundle recordings have suggested that the syndrome is, in fact, a type of pre-

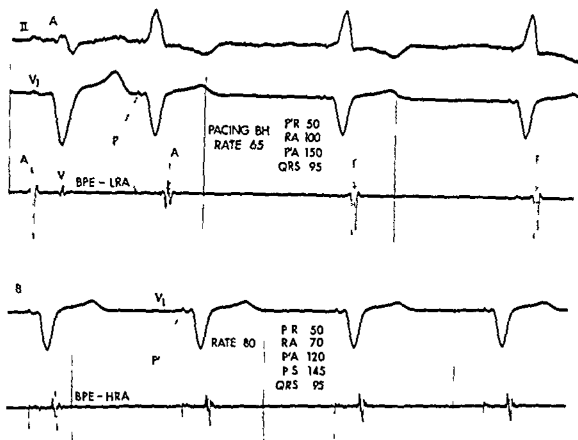


Fig 6 Case 1 Pacing bundle of HIS (BH) Bipolar electrogram is of the low right atrium (*BPE–LRA*) in Panel *A* and of the high right atrium (*BPE–HRA*) in Panel *B* Time lines are 1 second The P R in this instance is measured from the pacing impulse (*P*) to the onset of the R wave and equals 50 msec – the same as the H V interval Note that there is retrograde conduction to the atrium with earlier depolarization seen in the high right atrium The *QRS* duration is shorter with *BH* pacing (see text) Abbreviations as in Fig 5

at 193 per minute (Fig 7) At this rate the PR interval remained short at 120 msec the H V time increased slightly to 50 msec, but A V conduction continued on a 1 1 basis At one point (Fig 8) atrial pacing at 96 per minute resulted in supraventricular tachycardia at a rate of 240 per minute This happened frequently during the procedure and was terminated either by continued atrial pacing or by mechanical stimulation of the atrium with the pacing catheter Note that the SVT occurred following a spontaneous atrial premature beat The next pacing stimulus occurred very early at 200 msec, resulting in a markedly prolonged H V interval of 110 msec This delay in the His to Purkinje system was sufficient to set up a re entrant tachycardia

Case 3 His bundle studies on the older son (K A) revealed a short A H and a normal H V interval at all pacing rates including a maximum of 215 per minute (Fig 9) At this point occasional blocked beats were noted proximal to the bundle of His The A H interval increased slightly as the pacing rate increased Nevertheless even at rates of 215 per minute, it remained well within the normal resting limits as did the PR interval which measured 180 msec at this rate

Case 4 The younger son (T A) had a normal H V interval which remained so at rapid atrial pacing rates (Fig 10) The A H interval was at the lower limits of normal and increased slightly with progressive increase in pacing rates Even at rates exceeding 170 per minute there was a 1 1 A V conduction and the PR interval remained short That anomalous A V nodal bypass tracts exist and are utilized in an antegrade and retrograde fashion is suggested by Fig 11 which shows spontaneous ventricular premature contractions (VPC) associated with a markedly shortened ventricular atrial conduction time of 110 msec

Table I summarizes the conduction characteristics observed in this family The A H interval was short while the H V time was normal in all patients The A H interval in the mother and daughter remained essentially unchanged despite rapid atrial pacing The A H intervals in the two boys increased but only minimally during rapid atrial pacing K A s A H interval increased only 40 msec while going from a resting rate of 60 per

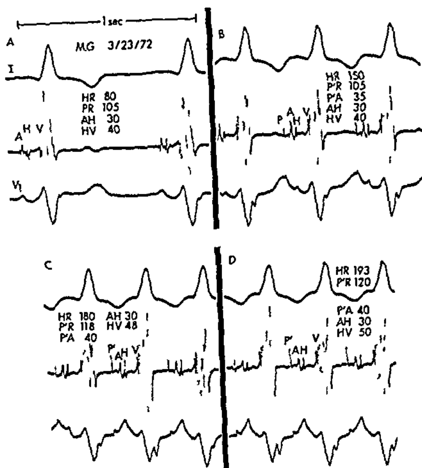


Fig 7 Case 2. HBE between Leads I and V in all panels The A H interval is short (30 msec) and remains unchanged with increasing atrial pacing rates At rates of 160 and 193 per minute the H V increases to 48 and 50 msec. respectively (Panels *C* and *D*) Abbreviations as in Fig 5

minute to a paced rate of 215 per minute and T A s A H increased 30 msec when his paced rate reached 170 per minute The H V interval increased slightly in M G with atrial pacing but remained within normal limits In the other three members of the family it remained unchanged

Discussion

ECG abnormalities are common accompaniments of familial myocardial disease[1-7] The abnormalities range from right bundle branch block (RBBB) LBBB and diffuse intraventricular conduction defects to first second and third-degree heart block to patterns of myocardial infarction to atrial ventricular and junctional arrhythmias The familial occurrence of conduction system disturbances unrelated to other familial cardiac disorders is being recognized with greater frequency The conduction disturbances are at times quite specific for a given family and include involvement of the sinus node[8] the A V node[9] the bundle of HIS[10-11] and the bundle branches[12,13] Prior to the pacemaker era these afflicted patients would progress to complete heart block and an early death

In 1952 Lown Ganong and Levine[22] described the syndrome of short PR interval normal QRS complex and paroxysmal SVT Thus far this syndrome has not been linked to a genetic defect Our patients did not have a normal QRS complex but the widened QRS was not related to a WPW syndrome Vector studies did not demonstrate selective slowing of the initial QRS vector and electrophysiologic combined with pacing studies ruled out functioning Kent bundles or Mahaim fibers Consequently we believe they represent examples of the L-G L syndrome

Although the mechanism producing these findings had been unclear and the cause of SVT unknown recent studies of A V conduction in man with His bundle recordings have suggested that the syndrome is in fact a type of pre

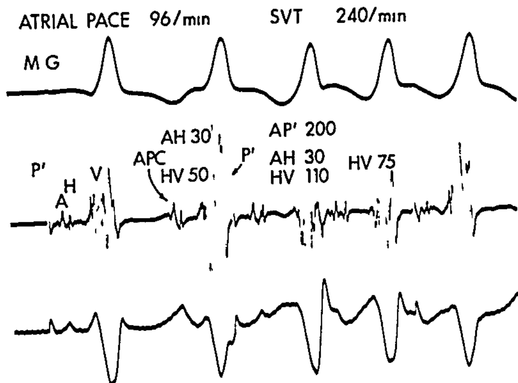


Fig 8 Case 2 During atrial pacing an APC followed by a pacing impulse 200 msec later resulted in prolongation of H V and a re entrant SVT Abbreviations as in Fig 5

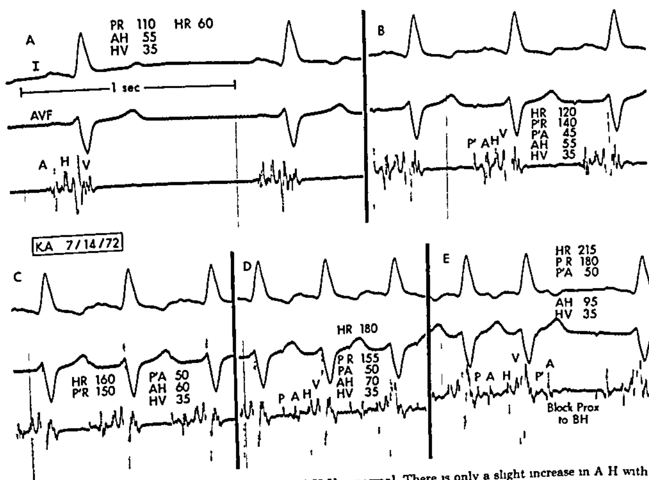


Fig 9 Case 3 The A H time is short (55 msec) and H V is normal There is only a slight increase in A H with increased pacing rates (Panels *C,D,E*) with no change in H V At rates of 215 per minute occasional beats were blocked proximal to BH (Panel *E*) Abbreviations as in Fig 5

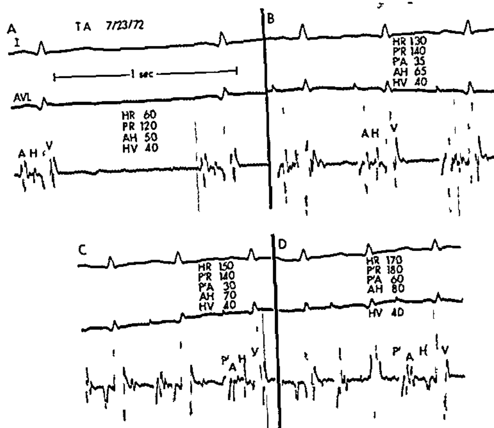


Fig 10 Case 4 The short A H time (50 msec) increases slightly with atrial rates of 170 per minute H V is normal. Abbreviations as in Fig 5

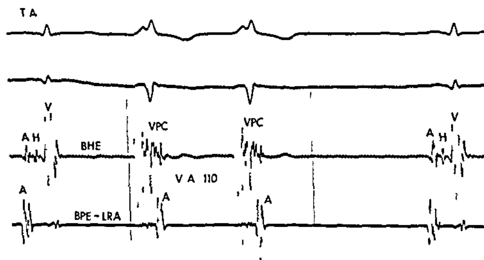


Fig 11 Case 4 From top to bottom Leads I aV_L BH electrogram and LRA electrogram The second and third beats are VPC's and demonstrate retrograde conduction to the atrium The short V A time (110 msec) suggests utilization of a nodal bypass tract Abbreviations as in Fig 5

excitation Castellanos and associates[3] studied three patients with short PR intervals and narrow QRS complexes who had paroxysmal tachycardias The shortening of the PR interval was related to a decrease in the A H time Caracta and associates[4] studied 18 patients with His bundle recordings, eight of whom had a history of SVT All of them had short A H and normal H V intervals Atrial pacing produced three types of responses (1) a progressive increase in A H interval similar to a normal response but to a much lesser degree, (2) an initial increase in A H, then a plateau response and, finally an increase in A H at higher pacing rates, (3) the least common occurrence was no significant increase in the A H interval Two of our patients (M A and M G) showed virtually no change in the A H time despite rapid atrial pacing rates of up to 208 per minute and two (T A and K A) demonstrated almost insignificant increase in A H time when going from sinus rates of 60 per minute to pacing rates of 170 and 215 per minute respectively Thus each of our patients had a type 3 response to pacing suggesting that the pattern of A V conduction was the same in all of our patients

Several mechanisms might be responsible for the shortened A V conduction time (1) accessory bundles (James bundles) bypass the A V node or most of the A V node and enter the His bundle directly, (2) conduction through the A V nodal tissue is markedly enhanced or propagated by preferential intranodal pathways, (3) absence of an A V node The type of response seen in our patients is certainly consistent with complete bypass of the A V node

The V A conduction time in T A was markedly shortened, suggesting that if anomalous bypass tracts exist they are utilized in both an antegrade and retrograde fashion This phenom enon was previously described by Castellanos[23] and Durrer[25] and their co workers

The mechanism of syncope was related to third degree heart block in the mother and daughter and possibly to marked sinus brady cardia in the two sons However, the occurrence of transient complete heart block in the sons cannot be ruled out The mechanism of complete heart block in the mother and daughter is not clear For that matter since we have not been able to restudy these patients we cannot localize the block as being proximal or distal to the bundle of His At the time of investigation our studies clearly indicated that intra atrial conduction was not impaired, A-H conduction was intact and His to Purkinje conduction was similarly unaffected Several mechanisms are possible (1) A pathologic process occurred in the bundle of His distal to the entrance of an anomalous James bundle (2) The anomalous bundle and the A V node were in close contiguity and both were subjected to the same disease process (3) Our patients did not have an A V node and the disease involved a pathway linking directly to the bundle of His (4) Patient M A had complete LBBB and quite possibly could have developed progressive disease of the right bundle branch producing complete heart block

We thought it unusual that complete heart block should develop in patient M G within 2 months of her bundle of His study which demon strated a normal H V interval, however, Kranz and Haft[6] reported four patients with ECG evidence of intraventricular conduction defects with normal H Q intervals who went on to develop complete heart block distal to the bundle of His within 1 to 4 days of the study

Sarachek and Leonard[12] brought up an inter esting possibility that the relationship between inherited sinus bradycardia and complete heart block may have any embryologic rationale The S A node, A V node and A V nodal–His bundle junction all develop during the first few months of gestation Malforming influences at that time could ostensibly affect development of all the above structures Familial heart block of adult onset and sinus bradycardia may then be caused by impairment of the S A and A V node the A V node to His bundle junction and the proximal bundle branches These lesions may progress as the patient approaches a certain age group at which time one can see the affect of these changes on a congenitally malformed and possibly vulnerable conduction system The presence of partial or complete bundle branch block appears to be a pre requisite or a precursor to the devel opment of complete heart block in the familial adult onset form of this disease Hence in the cases of both Sarachek and Leonard[12] and Lynch and associates[9] first and second degree heart block preceded complete heart block with evidence of progressive impairment of A V conduction This was not the case with our patients all of whom had very rapid A V conduc tion with short PR intervals

The nature of the cardiomegaly mild in three

of our patients is not known to us None of our patients had evidence for any neurologic muscular metabolic or infiltrative diseases often associated with myocardial hypertrophy Neither did they have any other known causes of hypertrophy such as rheumatic congential or coronary heart disease

Summary

Four members of a family presenting with sinus bradycardia a short P R interval intraventric ular conduction defects recurrent supraventricular tachycardia (SVT) syncope and cardiomegaly had His bundle studies and were found to have markedly shortened A H intervals (30 to 55 msec) with normal H V times (35 to 50 msec) Right atrial pacing at rates as high as 170 to 215 per minute failed to increase the A H or H V intervals significantly The data are compatible with the presence of an A V nodal bypass tract (James bundle) or even complete absence of an A V node Ventricular pacing and spontaneous ventricular premature beats resulted in a short ventriculoatrial conduction time (110 msec) suggesting that if A V nodal bypass tracts exist they are utilized in an antegrade and retrograde fashion None of the features of WPW syndrome was present

The mechanism of syncope in the mother and daughter was intermittent third degree heart block Both went on to develop permanent complete heart block despite electrophysiologic studies demonstrating 1 1 A V conduction at extremely rapid atrial pacing rates and both required implantation of permanent pacemakers The mechanism of syncope in the two brothers was possibly marked sinus bradycardia but transient complete heart block has not been ruled out Permanent pacemaker therapy was recommended for both

The nature of the cardiomegaly which was mild in three patients is not known Although not well documented several maternal relatives have had enlarged hearts SVT complete heart block, and syncope

REFERENCES

1 Evans, W Familial cardiomegaly Br Heart J 11 68 1949
2. Gaunt, R. T and Lecutier M A Familial cardiomegaly Br Heart J 18 251 1956
3. Beasley O C Familial myocardial disease Am J Med 29 4 6, 1960
4 Barold, S Linhart, J W Hildner F J Rywlin A., and Samet, P Familial cardiomyopathy A clinical hemodynamic and angiographic study in one family Chest 57 141 1970
5 Battersby E J and Glenner G G Familial cardiomyopathy Am J Med 30 38? 1961
6 Schrader W H., Pankey G A Davis R B and Theologides, A Familial idiopathic cardiomegaly Circulation 24 599 1961
7 Whitfield A. G W Familial cardiomyopathy Q J Med 30 119 1961
8 Spellberg R D Familial sinus node disease Chest 60 246 1971
9 Lynch H T Mohiuddin S Sketch M H., Krush A. J Carter S and Runco V Hereditary progressive atrioventricular conduction defect A new syndrome? J A. M. A. 225 1465 1973
10 Wright, F S Adams P Jr and Anderson R C Congential atrio ventricular dissociation due to complete or advanced atrioventricular heart block Am J Dis Child 98 72 1959
11 Wendkos M H and Study R S Familial congential complete A V heart block AM HEART J 34 138 1947
12 Sarachek N S and Leonard J J Familial heart block and sinus bradycardia Am J Cardiol 29 451 197?
13 Combrink J M Davis W H and Snyman H W Familial bundle branch block AM HEART J 64 397 1962
14 Gazes P C Culler R M Taber E and Kelly F T Congenital familial cardiac conduction defects Circulation 32 32, 1965
15 Schaal S F Seidensticker J Goodman R and Wooley C F Familial right bundle branch block left axis deviation complete heart block and early death Ann Intern. Med. 79 63 1973
16 Westlake R. E Cohen W., and Willis W W Wolff Parkinson White syndrome and familial cardiomegaly AM HEART J 64 314 1962
17 Harnischfeger W W Hereditary occurrence of the pre excitation (Wolff Parkinson White) syndrome with re entry mechanism and concealed conduction Circulation 19 28 1959
18 Massumi R. A Familial Wolff Parkinson White syndrome with cardiomyopathy Am J Med 43 951 1967
19 Schneider R G Familial occurrence of Wolff Parkinson White syndrome AM HEART J 78 34 1969
20 Noya M DelRio A and De Oya J C Wolff Parkinson White syndrome in a family Lancet 2 712 1971
21 Scherlag B J Lau S H Helfant R H., Berkowitz W D., Stein E and Damato A N Catheter technique for recording His bundle activity in man Circulation 39 13 1969
22. Lown B Ganong W F and Levine S A The syndrome of short PR interval normal QRS complex ans paroxysmal rapid heart action Circulation 5 693 1952
23. Castellanos A. Castillo C A Agha, A S and Tessler M His bundle electrograms in patients with short PR intervals narrow QRS complexes and paroxysmal tachycardias, Circulation 43 667 1971
24 Caracta A R Damato A N Gallagher J J., Josephson M E Varghese P J Lau S H and Westura E F Electrophysiologic studies in the syndrome of short PR interval, normal QRS complex Am J Cardiol 31 245, 1973
25 Durrer D Schulenburg and Wellens H J J Pre excitation revisited Am J Cardiol. 25 690 1970
26 Kranz, P D and Haft J Intraventricular conduction intervals during orthograde conduction in patients with complete heart block Circulation 46(Suppl II) 90 197?

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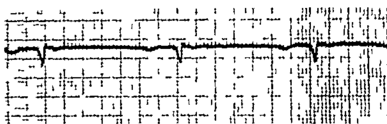


Fig 2 Case 1 ECG showing sinus bradycardia rate of 40 beats per minute

position A chest x ray was performed and showed the hiatus hernia trapped within the chest as shown in Fig 4 After 10 minutes the rate returned to normal and the chest x ray showed that the hernia was reduced At operation a large mixed sliding and paraesophageal hiatus hernia was repaired Subsequent follow up has shown no recurrence of the arrhythmia

Case 3 A 56-year old man presented with gross esophageal reflux Serum investigations and resting and exercise ECG s were all found to be normal No postural hypotension could be demonstrated He had no history of cardiac disease At esophagoscopy esophagitis and gross reflux were demonstrated During the patient s stay in hospital three episodes of sinus bradycardia were recorded all of which were precipitated by lying down These attacks were terminated by atropine which reversed the bradycardia of rate 40 to the normal rate of 76 At operation the patient s large sliding and paraesophageal hiatus hernia (Fig 5) was repaired and there has been no subsequent recurrence of the arrhythmia

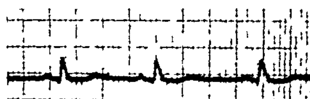


Fig 3 Case 1 ECG showing normal rate (7 beats per minute)



Fig 4 Case 2 Chest x ray showing hiatus hernia *trapped* within the chest

Discussion

The majority of hiatus hernias produce no symptoms Very rarely they may produce pain on effort Occasionally they may produce substernal or precordial discomfort when the patient is bending or lying on the left side It is probable that most symptoms attributed to hiatus hernias are actually due to reflux esophagitis Resemblances may be due to the transmission of pain impulses from the esophagus over cord segments which are similar to those carrying pain impulses from the heart Particularly with large hernias which cause displacement of thoracic structures there may be dyspnea or palpitations Associated spasm of the diaphragm may produce referred phrenic pain in the left shoulder region and this may be projected downward into the arm and be associated with palpitation thus simulating cardiac disease

Changes in posture can produce effects on heart rate Thus on adopting the supine position cardiac output increases and heart rate will fall In fact usually this accounts only for a small reduction in basal rate yielding a rate a few beats below normal value for a short time However there are cardiovascular reflexes which can profoundly affect heart rate and can produce significant bradycardia These reflexes are initiated by stimulation of the nerves or nerve endings in the ventricles left atria and epicardium Stimulation of receptors located in the epicardium is favored as the explanation of production of bradycardia in hiatus hernias

Brief occlusion of the outflow from the cannu

Sinus bradycardia with hiatus hernia

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Three patients were seen who had large mixed sliding and paraesophageal hiatus hernias associated with intermittent sinus bradycardia In all cases the bradycardia was abolished by atropine pointing to vagal mediation In no case did the arrhythmia recur after surgical repair of the hernia These cases are considered worthy of report since sinus bradycardia has not been recorded in association with hiatus hernia

Case reports

Case 1 The patient a 65 year old man was admitted to hospital with pain in the left hypochondrium intermittently radiating into the left arm The pain was unaffected by exercise but was brought on by adopting the supine position He complained also of water brash and this was related to food being particularly severe after a large meal It was relieved by antacids and polymethylsiloxane This symptom complex had been present for 3 years but had become progressively worse especially in the last 3 months before presentation In addition for the 6 months prior to admission he complained of intermittent attacks of dizziness also precipitated by lying down It had been noticed by a medical attendant that his pulse rate had dropped to 40 during one of these attacks The patient had complained of dizziness but there was no syncope

Examination on admission revealed no abnormalities save some epigastric tenderness The cardiovascular system was normal Both resting and exercise electrocardiograms (ECG s) were blameless of normal axis and in sinus rhythm There was no postural hypotension Serum biochemistry was normal too

Barium swallow was performed and showed gross reflux with a large mixed sliding and paraesophageal hiatus hernia (Fig 1) Stomach and duodenum were normal Esophagoscopy showed esophagitis and much regurgitation but there was no stenosis or tumour

During his stay in hospital preoperatively of 6 days duration he had 16 attacks of bradycardia which were always precipitated by lying down The ECG presented in Fig 2 shows a trace during one of these attacks the rate being 40 beats per minute and the ECG presented in Fig 3 shows his normal rate (75 beats per minute) The rate was fixed at 40 per minute and was unaffected by exercise in the erect position but atropine caused it to increase



Fig 1 Case 1 Barium swallow showing a large mixed sliding and paraesophageal hiatus hernia

On very few occasions the bradycardia persisted on his reaching the standing position During these times the chest x ray showed that the hiatus hernia remained trapped within the chest After 20 minutes the rate returned to normal and the chest x ray showed that the hernia was reduced This sequence was demonstrated some five times before operation

At operation an extremely large hiatus hernia was discovered and repaired Postoperative recovery was uneventful and the pulse rate remained consistently in his normal range of 80 per minute No episodes of bradycardia have been experienced by the patient in over 18 months of follow up

Case 2 The patient was a 52 year old woman who experienced transient episodes of sinus bradycardia on adopting the supine position This was in the total absence of overt cardiac disease Resting and exercise ECG s were normal as was serum biochemistry No postural hypotension could be demonstrated In her case the sinus bradycardia caused no symptoms and was a chance finding by a medical attendant Four episodes of bradycardia were recorded electrocardiographically while she was in hospital On one recorded occasion the bradycardia persisted when she assumed the standing

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Echocardiographic diagnosis of mitral regurgitation in congestive cardiomyopathy

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Echocardiography has made a valuable contribution to the understanding of congestive hypertrophic and infiltrative cardiomyopathies [1] The echocardiographic findings which have been described in congestive cardiomyopathy are a dilated left ventricular cavity poor interventricular septal and posterior wall motion and normal wall thickness [1,3] Normal or increased septal motion in the dilated left ventricle with poor posterior wall motion has been interpreted as evidence for segmental myocardial disease namely focal myocardial damage with intact septal function which would exclude congestive cardiomyopathy We have studied eight patients with congestive cardiomyopathy diagnosed by cardiac catheterization who had an apparently normal or increased septal motion on the echocardiogram This pattern correlated with the presence of significant mitral regurgitation

Patient selection and methods

Eighteen patients presenting with congestive heart failure were diagnosed as having congestive cardiomyopathy on the basis of clinical evaluation cardiac catheterization and angiocardiography Patients with obstructive coronary disease aortic valve disease prosthetic valves or mitral stenosis were excluded

Two independent observers evaluated the left ventriculograms for mitral regurgitation and grouped the studies into four categories (1) no regurgitation (2) mild small amount of regurgitant contrast but not enough to delineate the left atrium (3) moderate clear visualization of the left atrium but never reaching the density of the left ventricle and (4) severe the left atrium became as densely opacified as the left ventricle Both observers agreed with each other on all studies except one that was interpreted as moderate by one and severe by the other

Echocardiograms were performed with an Ekoline 20 echocardiograph machine utilizing a 10 cm focus transducer at 2 25 MHz with a repetition rate of 1 000 per second The tracings were recorded on a Honeywell 1856 recorder From the tracings the following measurements were made

1 *Left ventricular end diastolic diameter (Dd)* The distance between the left septal surface and the endocardium of the posterior wall below the mitral valve at the R wave of the ECG (normal less than 5 4 cm)
2 *Left ventricular end systolic diameter (Sd)* The shortest simultaneous distance between septal and posterior wall endocardium in systole
3 *Left atrial size in systole* (maximum inner diameter normally less than 3 8 cm)
4 *Mitral valve diastolic (E F) slope* (normal 60 to 150 mm per second)
5 *Aortomitral discontinuity (AMd)* The anteroposterior distance between the systolic closure of the mitral valve (C point) and the posterior wall of the aortic root at the beginning of systole (normal less than 8 mm) (see Fig 1)
6 *Left ventricular posterior wall thickness in diastole prior to the a dip* (normal 0 7 to 1 1 cm)
7 *Left ventricular posterior wall motion* The excursion of the posterior endocardium from

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Fig 5 Case 3 Barium swallow showing large sliding and paraesophageal hiatus hernia

lated coronary sinus in the open chest anesthetized dog caused a rise in coronary venous pressure and bradycardia [1] The bradycardia was abolished by intravenous atropine This response was abolished by cutting the cervical vagi and reversibly abolished by cooling them to less than 7° C Distension of the left atrium with or without concomitant pulmonary venous distension has been found to cause bradycardia in anesthetized dogs Both these mechanisms are not thought to be relevant to the mechanism of production of bradycardia in hiatus hernias It has been found that 25 to 100 μg of acetylstrophanthidin to the epicardium of the left ventricle of anesthetized and unanesthetized dogs caused bradycardia [3] The response developed after an average latency of 8 seconds and lasted up to 12 minutes Cooling the cervical vagi to 8 to 10° C or prior application of 1 per cent procaine hydrochloride to the epicardium of the heart blocked the response The response was therefore a reflex of the sensory receptors being located in the surface layers of the left ventricle Electrophysiological recordings from simple and multifiber preparations of the right recurrent cardiac nerve show that the receptors for this reflex are the mechanoreceptors whose fibers belong to the C group This was confirmed by Bergel and Makin [4] who showed that epicardial stimulation of the left ventricle with nicotine in open chest anesthetized dogs produced a fall in heart rate mediated reflexly by the vagus

The extreme similarity of the changes following epicardial stimulation to those seen in the fainting reaction with particular reference to bradycardia raises the possibility of a more than fortuitous resemblance It must be stressed that none of the three patients had at any time significant hypotension or any of the other symptoms of fainting Furthermore the persistence of the bradycardia and the fact it disappeared on adopting the erect posture save on those occasions during which the hernia remained within the chest radiologically points to the pressure effect on epicardial receptors as being the most likely explanation The fact that the bradycardia was abolished by atropine points to its vagal mediation

Summary

Three cases of large mixed sliding and paraesophageal hiatus hernias are described These were associated with episodes of sinus bradycardia The bradycardia was abolished by atropine pointing to vagal mediation After surgical repair of the hernia there was no recurrence of the arrhythmia These cases have been considered worthy of report since sinus bradycardia has not been recorded specifically in association with hiatus hernias

REFERENCES

1 Muers M F and Sleight P The reflex cardiovascular depression caused by occlusion of the coronary sinus in the dog J Physiol **221** 259 1970
2 Edis A J Donald D E and Shepherd J T Cardiovascular reflexes from stretch of pulmonary vein-atrial junctions in the dog Circ Res **27** 1091 1970
3 Sleight P Lall A and Muers M Reflex cardiovascular effects of epicardial stimulation by acetylstrophanthidin in dogs Circ Res **25** 705 1969
4 Bergel D H and Makin G S Central and peripheral cardiovascular changes following chemical stimulation of the surface of the dogs heart Cardiovasc Res **1** 80 1967

Table I Echocardiographic measurements on 18 patients with congestive cardiomyopathy*

	L V cavity		*LA*	*M V E F slope*		*LVPW*		*I V septum*			
	Dd (cm)	*Sd (cm)*	*Mx (cm)*	*(mm/sec)*	*AMd (mm)*	*DTH (cm)*	*M (cm)*	*DTH (cm)*	*STHg (%)*	*M (cm)*	*Angiogram*
Normal	40-54		< 38	60 150	< 8	0711	10-14	08-12	30	04-07	
1 P H	70	64	40	80	30	10	09	11	10	01	Mo
2 R G	80	68	40	170	20	07	06	08	0	08	Mo
3 A G	80	70	36	160	1.	1.0	09	09	0	0	Mo
4 L E	65	58	54	80	14	08	05	09	0	05	Mo
5 F B	66	52	42	80	18	07	08	06	0	06	Se
6 J A	74	62	38	100	20	08	07	08	0	07	Mo
7 M M	7?	58	39	74	10	08	06	09	0	0	None
8 W S	76	68	46	1?0	20	0.8	08	0.8	0	0	None
9 M M	58	54	50	100	1?	07	08	08	0	02	Mo
10 G B	62	54	42	90	14	10	08	10	0	0	Mi
11 P W	74	69	46	82	17	0.8	0.5	09	0	04	Se
12 Ch M	72	65	43	150	15	08	08	09	0	0	Mi
13 G B	60	47	38	90	16	08	0.9	09	20	02	Mi
14 Ch. R	80	7.5	42	87	14	10	07	11	0	0	Mo
15 Ch O	7.5	6.8	41	100	18	09	0.8	10	10	03	Mi
16 B R.	85	70		120		0.8	08	08	10	1.2	Mo
17 R G	70	61	40	95	14	08	09	08	0	04	Mo
18 B S	78	60	50	120	14	09	09	10	20	08	Mo
Mean	7.2	6.2	4.3	105	165	08	076	088	3.94	0.35	
± SE	± 017	± 017	± 01?	± 6.8	± 11	± 00?	± 003	± 003	± 160	± 008	

Abbreviations LV cavity left ventricular cavity Dd diastolic diameter Sd systolic diameter LA left atrium MV mitral valve AMd, aortomitral discontinuity LVPW left ventricular posterior wall TH thickness M motion IV septum, interventricular septum *DTH diastolic thickness STHg*, systolic thickening Mi, mild Mo moderate Se severe

peak of the R wave of the ECG to its most posterior point in systole (normal 0 4 to 0 7 cm)

11 Passive septal motion = septal motion −(STH−DTH)

Results

The echocardiographic measurements on the 18 patients with congestive cardiomyopathy are shown in Table I They *reveal dilatation of the* left ventricle (Dd 7 2 ± 0 17 cm) and left atrium (maximum diameter 4 3 ± 0 12 cm) In one patient the left atrial echogram could not be evaluated The mitral valve diastolic (E F) *slope* was usually normal (105 ± 6 8 mm per second)

Aortomitral discontinuity was increased in all 17 patients in whom it could be evaluated (16 5 ± 1 1 mm) Left ventricular posterior wall motion was decreased in all patients (0 76 ± 0 03 cm) with normal posterior wall thickness (0 8 ± 0 22 cm) Interventricular septal thickness was normal in all 18 patients (0 88 ± 0 03 cm) Systolic thickening of the septum was absent in 13 patients and was reduced in all others (3 94 ± 1 60 per cent)

Septal motion was absent or *decreased in 10* patients (Fig 3) six of whom had mild or no mitral regurgitation Two of these patients had left bundle branch block Four had moderate mitral regurgitation on the angiogram Eight *patients had normal or increased septal motion* (Fig 4) and all of these patients had significant *mitral* regurgitation on angiography (Fig 5) Correction of septal motion for thickening (passive septal motion) did not significantly change the results

Septal systolic thickening was 50 ± 2 41 per cent (S E M) (range 30 to 70 per cent) in our 20 normal subjects 73 ± 2 78 per cent (range 60 to 86 per cent) in the eight patients with left ventricular *volume overload* and 70 ± 7 61 per cent (range 58 to 100 per cent) in the five patients with *coronary* disease and normal septa

Discussion

In these 18 patients with congestive cardiomyopathy three features were constant in the echo *cardiogram of the left* ventricle namely a dilated cavity reduced posterior wall motion and decreased septal systolic thickening (Table I) In

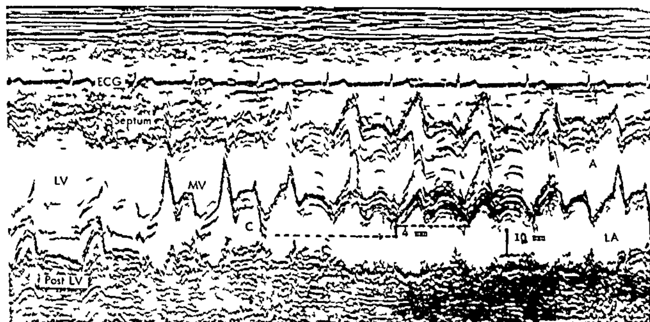


Fig 1 Normal echocardiogram *A* Aortic root *C* mitral closure point *ECG* electrocardiogram *LV* left ventricle *LA* left atrium *MV* mitral valve *Post LV* posterior left ventricular wall The dashed line indicates the levels of the mitral closure and the posterior aortic wall for determination of aortomitral discontinuity (*AMd*) In this patient the AMd measures 4 mm

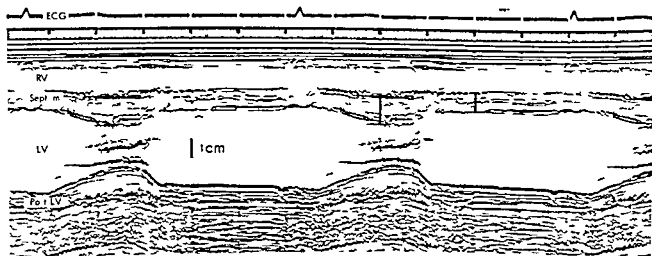


Fig 2 Normal echocardiogram The dark lines across the septum indicate the systolic and diastolic septal thickness The systolic thickening is 50 per cent Abbreviations as in Fig 1

the diastolic position at the peak of the R wave to its most anterior position in systole (normal 1 0 to 1 4 cm)

8 *Septal diastolic thickness (DTH) prior to the a dip* (normal 0 8 to 1 2 cm)

9 *Septal systolic thickening (STHg)* The per cent change of septal thickness during systole with the use of the formula

$$STHg = \frac{STH - DTH}{DTH} \times 100$$

Where STH is the maximum systolic thickness of the septum (Fig 2) Septal systolic thickening was also measured on the echocardiograms of (1) 20 normal subjects (2) eight patients with left ventricular volume overload due to aortic or mitral regurgitation and normal coronaries and (3) five patients with coronary disease and segmental akinesis or dyskinesis on the ventriculogram normal left anterior descending coronary artery and no valvular regurgitation

10 *Septal motion* The excursion of the left septal endocardium from end diastole at the

Four patients with significant mitral regurgitation showed decreased or absent septal motion and there were no detectable echocardiographic findings to suggest mitral regurgitation in these patients On the other hand no patient in this series showed apparently normal or increased septal motion in the absence of significant mitral regurgitation

The abnormal pattern of septal motion associated with left bundle branch block [3, 5] was not seen in the two patients with this conduction defect since contraction of the septum was not detectable

Analysis of septal motion by itself could not distinguish congestive cardiomyopathy with significant mitral regurgitation and passive septal motion from a dilated left ventricle due to myocardial infarction with a compensatory increase in septal motion However in the former condition there was reduced septal systolic thickening whereas the latter showed increased septal systolic thickening (Fig 6) Volume overload of the left ventricle with normal or hypertrophied myocardium would also increase septal systolic thickening (Fig 7)

Reduced septal systolic thickening has been observed in hypertrophic cardiomyopathy [7] In this entity asymmetric hypertrophy of the septum and normal or small LV cavity size permit little difficulty in differential diagnosis

Reduced septal thickening is also a feature of infiltrative cardiomyopathy such as that due to amyloid [8] Increased septal and posterior wall thickness and a small left ventricular cavity in this syndrome make it easily recognizable

An abnormal aortomitral discontinuity has been proposed as indirect evidence for mitral regurgitation We found an abnormally increased value in the 17 patients with congestive cardiomyopathy in whom it could be measured regardless of mitral valve competence and it is probably related merely to dilatation of the left ventricle and to transducer position on the chest wall Our study does not support previous observations of abnormal systolic motion of the mitral valve as evidence of mitral insufficiency in congestive cardiomyopathy

These observations confirm previous studies on congestive cardiomyopathy which have shown that a dilated left ventricle with normal wall thickness and reduced septal and posterior wall motion are the major echocardiographic features

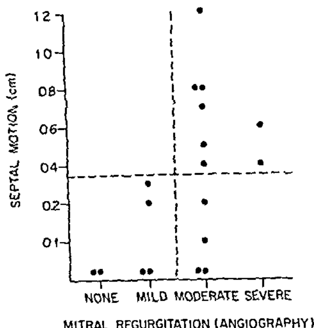


Fig 5 Diagram showing the correlation between septal motion and degree of mitral regurgitation The vertical dashed line separates the cases with no or mild regurgitation from moderate and severe The horizontal dashed line is drawn just below the lower limit of normal septal motion

of this syndrome We further suggest that an apparently normal or increased septal motion with reduced or no septal systolic thickening is also compatible with congestive cardiomyopathy and when present is evidence for coexistent left ventricular volume overload usually due to significant mitral regurgitation Reduced or absent septal systolic thickening distinguishes this syndrome from segmental myocardial disease with intact septal function

Summary

Eighteen patients with congestive cardiomyopathy were studied by echocardiography and cardiac catheterization Patients with coronary disease on angiography or primary valvular disease were excluded Six patients showed mild or no mitral regurgitation in 12 others the degree of mitral regurgitation was moderate or severe

The echocardiographic features in these patients were (1) a dilated left ventricle (LV) (2) normal LV wall thickness (3) reduced LV posterior wall motion and (4) reduced or absent systolic thickening of the interventricular septum (IVS)

IVS motion was reduced in 10 patients and

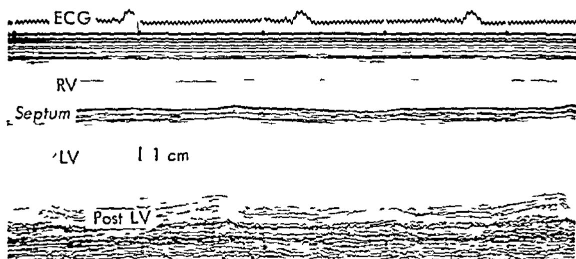


Fig 3 Echocardiogram of a patient with congestive cardiomyopathy without mitral regurgitation (Case 12 Table I) Note the absence of both septal motion and systolic thickening There is also biventricular dilatation Abbreviations as in Fig 1

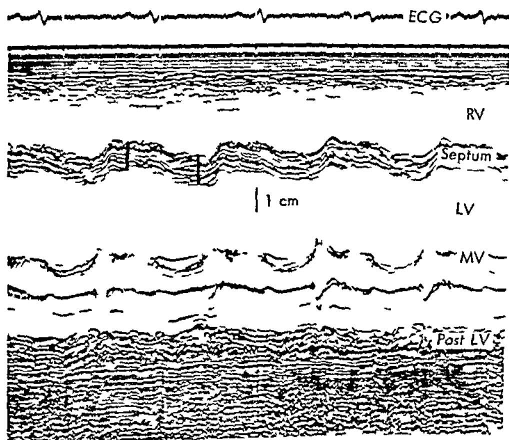


Fig 4 Echocardiogram of a patient with congestive cardiomyopathy and severe mitral regurgitation (Case 6 Table I) Note the apparent normal septal motion and no systolic thickening as indicated by the dark lines

10 patients septal motion was reduced or absent as previously reported In the other eight patients septal motion was either normal or increased however an apparent normal septal motion without systolic thickening suggests a passive motion that is not due to contraction of the myocardium In these eight patients there was significant mitral regurgitation This volume overload of the left ventricle may make the septum move passively toward the right ventricle in diastole during ventricular filling and posteriorly again as the ventricular volume decreases in systole A similar pattern of septal motion in congestive cardiomyopathy would probably also be produced by left ventricular volume overload due to a variety of causes

Four patients with significant mitral regurgitation showed decreased or absent septal motion and there were no detectable echocardiographic findings to suggest mitral regurgitation in these patients On the other hand no patient in this series showed apparently normal or increased septal motion in the absence of significant mitral regurgitation

The abnormal pattern of septal motion associated with left bundle branch block [3,15] was not seen in the two patients with this conduction defect since contraction of the septum was not detectable

Analysis of septal motion by itself could not distinguish congestive cardiomyopathy with significant mitral regurgitation and passive septal motion from a dilated left ventricle due to myocardial infarction with a compensatory increase in septal motion However in the former condition there was reduced septal systolic thickening whereas the latter showed increased septal systolic thickening (Fig 6) Volume overload of the left ventricle with normal or hypertrophied myocardium would also increase septal systolic thickening (Fig 7)

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These observations confirm previous studies on congestive cardiomyopathy which have shown that a dilated left ventricle with normal wall thickness and reduced septal and posterior wall motion are the major echocardiographic features of this syndrome We further suggest that an apparently normal or increased septal motion with reduced or no septal systolic thickening is also compatible with congestive cardiomyopathy and when present is evidence for coexistent left ventricular volume overload usually due to significant mitral regurgitation Reduced or absent septal systolic thickening distinguishes this syndrome from segmental myocardial disease with intact septal function

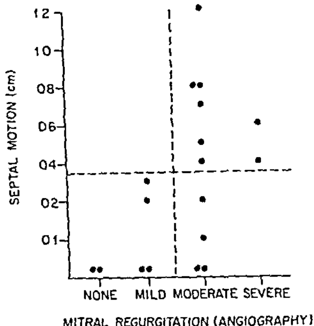


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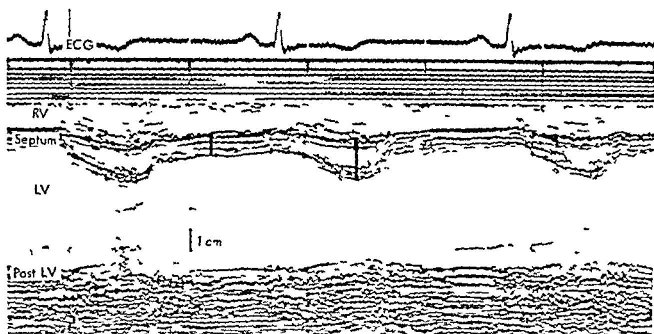


Fig 6 Echocardiogram of a patient with a posterior myocardial infarction Septal systolic thickening is 100 per cent as indicated by the dark lines The posterior wall motion is reduced

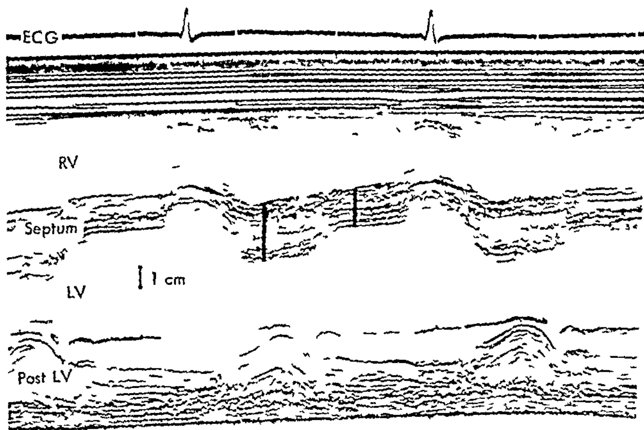


Fig 7 Echocardiogram of a patient with combined aortic stenosis and insufficiency The septal systolic thickening is 75 per cent Note the concentric hypertrophy of the left ventricle dilated left ventricular cavity and prominent atrial deflection in the septum

appeared normal' or increased in another eight all of whom showed moderate or severe mitral regurgitation on angiography

It is concluded that an apparent normal or increased motion of the IVS with reduced or absent systolic thickening in congestive cardiomyopathy is evidence for coexistence of significant mitral regurgitation

Reduced or absent systolic thickening can distinguish these patients from those with segmental myocardial disease and normal septa or dilated LV s due to volume overload

The author wishes to thank Drs Rex N MacAlpin and Abdul S Abbasi for their advice and encouragement Drs. Cornelius J Bos and Bruce M Barack for reviewing the angiograms Mrs Nancy Ellis for technical assistance and Mrs. Rita Bachtold and Mrs. Pat Ritter for the secretarial support

REFERENCES

1 Abbasi A S Chahine R A MacAlpin R N and Kattus A A Left ventricular function in congestive cardiomyopathy Chest 62 357 1972
2 Abbasi A S Chahine R A, MacAlpin R N and Kattus A A Ultrasound in the diagnosis of primary congestive cardiomyopathy Chest 63 937 1973
3 Corya B C Feigenbaum H Rasmussen S and Black M J Echocardiographic features of congestive cardiomyopathy compared with normal subjects and patients with coronary disease Circulation 49 1153 1974
4 Assad Morell J L Tajik A. J and Giuliani R R Echocardiographic analysis of the ventricular septum Prog Cardiovasc Dis 17 219 19 4
5 Abbasi A S MacAlpin R N Eber L M and Pearce M L. Echocardiographic diagnosis of idiopathic hypertrophic cardiomyopathy without outflow tract obstruction Circulation 46 897 1972
6 Abbasi A S MacAlpin R N Eber L M and Pearce M L. Left ventricular hypertrophy diagnosed by echocardiography N Engl J Med 289 118 1973
7 Henry W L Clark C E and Epstein S E Asymmetric septal hypertrophy (ASH) Echocardiographic identification of the pathognomonic anatomic abnormality of I H.S S Circulation 47 225 1973
8 Tajik A J and Giuliani, R R Echocardiographic observations in idiopathic hypertrophic subaortic stenosis Mayo Clin Proc 49 89 1974
9 Abbasi A S Ellis, M and Child J C Echocardiographic features of infiltrative cardiomyopathy J Clin Ultrasound 2 291 1974
10 Levisman J A Child J C Abbasi, A S., and MacAlpin R N Echocardiographic findings in amyloid heart disease Circulation (abstr) 52 II 208 1975
11 Rossen R M Goodman D J Ingham R E and Popp R L. Ventricular systolic septal thickening and excursion in idiopathic hypertrophic subaortic stenosis N Engl J Med 291 1317 1974
12 Johnson M L Kisslo J Warren S G., and Behar V S Echocardiographic diagnosis of mitral apparatus dysfunction with mitral insufficiency J Clin Ultrasound 2 237 1974
13 Dillon J C., Chang S and Feigenbaum H Echocardiographic manifestations of left bundle branch block (abst) Circulation 48 (Suppl. IV)IV-126 1973
14 McDonald I G Echocardiographic demonstration of abnormal motion of the interventricular septum in left bundle branch block, Circulation 48 272 1973
15 Abbasi, A S Eber L M MacAlpin R N., and Kattus A. A Paradoxical motion of the interventricular septum in left bundle branch block Circulation 49 423 1974
16 Wilward D K McLaurin L, P and Craige E Echocardiographic studies of the mitral valve in patients with congestive cardiomyopathy and mitral regurgitation AM HEART J 85 413 1973

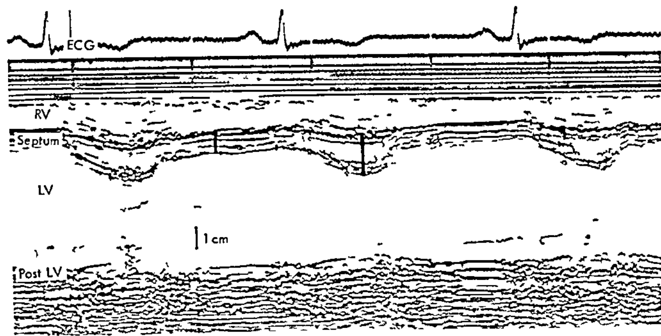


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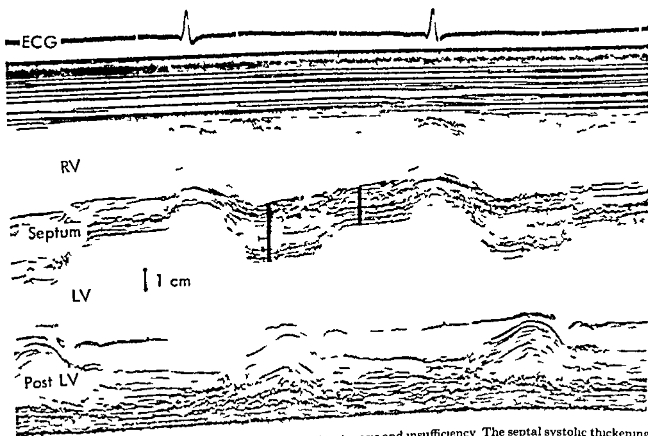


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Reduced or absent systolic thickening can distinguish these patients from those with segmental myocardial disease and normal septa or dilated LV s due to volume overload

Table I Interval between catheterization and surgery (mean ± S D)

	No of cases	Age at cardiac catheterization (mo)	Interval between cardiac catheterization and surgery (mo)
Group A Pp/Ps < 0 5	23	56 1 ± 10 1	11.3 ± 5 [illegible]
Group B Pp/Ps 0 5 0 8	31	31 3 ± 17.8	10 4 ± 3.5
Subgroup B 1 (diminished VSD size)	13	34.2 ± 1[illegible].9	10 4 ± 3.2
Subgroup B 2 (unchanged VSD size)	18	28 3 ± 16 3	10 4 ± 3 8
Group C Pp/Ps ≧ 0 8	33	26 8 ± 17 1	7 4 ± 4 8

Table II Hemodynamic data and VSD size (mean ± S D)*

	Size of VSD (cm /M BSA)	Pp/Ps	Qp/Qs	Rp/Rs
Group A Pp/Ps < 0 5	0 6 ± 0 4	0.31 ± 0 04	1 73 ± 0 40	0 14 ± 0 03
Group B Pp/Ps 0 5 0 8	0 9 ± 0 5	0 62 ± 0 08	2 6[illegible] ± 0.84	0 21 ± 0 09
Subgroup B-1 (diminished VSD size)	0 5 ± 0 2	0 61 ± 0 08	2 [illegible]6 ± 0 82	0 17 ± 0 06
Subgroup B 2 (unchanged VSD size)	1 2 ± 0 3	0 63 ± 0 09	2 51 ± 0 84	0 24 ± 0 09
Group C Pp/Ps ≧ 0 8	2 5 ± 1 2	0 96 ± 0 07	2 03 ± 0 49	0 42 ± 0 14

BSA body surface area Pp/Ps, the ratio of systolic pulmonary artery pressure to systolic systemic artery pressure Qp/Qs the ratio of pulmonary blood flow to systemic blood flow Rp Rs, the ratio of total pulmonary vascular resistance to systemic vascular resistance

pulmonary artery was entered in all cases allowing calculation of total pulmonary vascular resistance (TPR) Calculations and analyses were made with conventional Fick formulas The size of the VSD was measured by the same surgeon in the same manner On total bypass with the aorta cross clamped the heart was fibrillated spontaneously or electrically With the cardiac chambers emptied the diameters of the defect were measured carefully with compasses in two dimensions a longer axis and its perpendicular axis and the area of the defect was calculated as a circle or an ellipse

Results

The patients were divided into three groups according to the ratio of systolic pulmonary artery pressure to systolic systemic artery pressure (Pp/Ps) Group A Pp/Ps < 0 5 Group B Pp/Ps 0 5 to 0 8 Group C Pp/Ps ≧ 0 8 (Table I) The mean values of hemodynamic data and size of VSD in each group are summarized in Table II In Fig 1 Pp/Ps has been plotted against the size of the defect per square meter of body surface area In general there is some correlation between the relative defect size and the relative pulmonary pressure among the patients in Group A and Group C but patients in Group B scattered rather unpredictably below the expected zone of prediction The vast majority of the VSDs were below 0 8 cm per square meter in patients of Group A and over 1 6 cm² per square meter in patients of Group C but in 45 per cent of patients of Group B the defect was below 0 8 cm² per square meter—the same range as Group A and the remaining were between 0 8 to 1 6 cm² per square meter of BSA

According to well accepted principles governing the hemodynamics of VSD the size of most of VSDs in Group B should be above 0 8 cm per square meter and some correlation between Pp/Ps and the size of the VSD should be found However in our study 45 per cent of the patients in Group B had defects below 0 8 cm per square meter at the time of surgery and no correlation existed between Pp/Ps determined at the time of diagnostic catheterization and the size of VSD found at surgery

Lucas and co workers[14] reported in 1961 that all patients with VSD smaller than 0 8 cm² per square meter had Pp/Ps less than 0 33 Lynfield and co workers[5] showed in 1961 that patients with defects smaller than 1 cm² per square meter had normal or near normal pulmonary artery pressures and in patients with defects smaller than 2 cm per square meter significant correla

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Subgroup B 2 (unchanged VSD size)	1 [illegible] ± 0 3	0 63 ± 0 09	2.51 ± 0 84	0.24 ± 0 09
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Ventricular septal defect. Selection of patients and timing for surgery

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Extensive studies on the natural history of ventricular septal defect (VSD) reveal a significantly high incidence of spontaneous closure and spontaneous decrease in size.[1-8] What is not known is how to predict which VSD can be expected to close or decrease in size spontaneously. Consequently, the selection of patients for surgery is a subject for debate. There is a unanimous agreement on the expectant management of patients with the ratio of systolic pulmonary artery pressure to systolic systemic artery pressure (Pp/Ps) < 0.5 without risk of development of pulmonary vascular disease,[1, 3, 11] anticipating spontaneous closure. The high risk of development of pulmonary vascular disease in patients with $Pp/Ps \geq 0.8$ is also widely accepted.[9-13] Patients with Pp/Ps 0.5 to 0.8 constitute a special group as to decision on the type of management. The purpose of this paper is to report the fact that in almost one half of this particular group of patients the VSD will decrease in size spontaneously, and underline the value of various clinical parameters to predict it.

Because of the case load of the surgical department in our institution, a mean interval of 10 months exists between catheterization and surgery in the majority of patients in our study group. At surgery, we have been surprised frequently by the unexpectedly small sized VSD, as one would anticipate from the catheterization data. This phenomenon stimulated our interest to study retrospectively all the cases with isolated VSD that were operated upon in the first 5 years of life, to determine whether the size of the VSD would decrease to such an extent in such a short time and whether it could have been predicted clinically.

Materials and methods

Eighty seven cases of isolated VSD that were operated upon between 1970 and 1974 were reviewed. Clinical examinations, including chest x-rays, electocardiogram (ECG) and phonocardiogram (PCG), were performed both at the time of diagnostic catheterization and at surgery. There was approximately a 10 month interval between catheterization and surgery (Table I). Catheterization was performed under light sedation with hydrochloride pethidine and sodium secobarbital. Pressures were recorded on a Hewlett Packard recorder with a Statham P23H transducer located at one third the chest thickness below the sternum. Oxygen saturations and contents were assessed with an IL meter (Model 113) and Van Slyke analysis. Oxygen consumption was calculated in all instances with a figure of 180 ml. per square meter per minute. The

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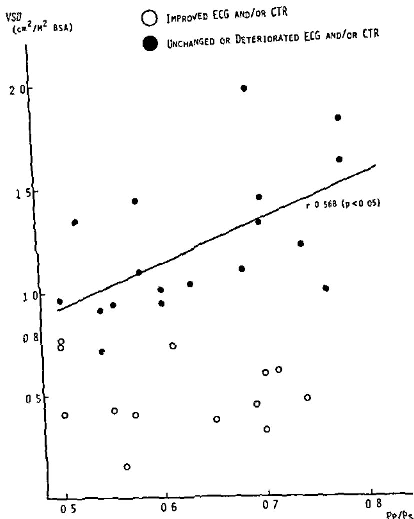


Fig 2 Relationship between Pp/Ps and size of VSD in Group B with Pp/Ps 0 5 to 0 8 Significant correlation exists between Pp/Ps and the size of VSD in the group with unchanged or deteriorated ECG and/or CTR Abbreviations *ECG* electrocardiogram *CTR* cardiothoracic ratio

with improved ECG and/or cardiothoracic ratio (CTR) was less than 0 8 cm per square meter On the other hand the size of defect in all but one case with unchanged or deteriorated ECG and/or CTR was above 0 8 cm per square meter and a significant correlation existed between Pp/Ps and the size of VSD in the group with unchanged or deteriorated ECG and/or CTR ($r = 0\,568$ $p < 0\,05$) Also significant correlation existed between Qp/Qs and size of VSD in the group with unchanged or deteriorated ECG and/or CTR ($r = 0\,802$ $p < 0\,01$) (Fig 3) These correlations between VSD size and Pp/Ps Qp/Qs are in agreement with the hemodynamics of VSD reported by many others Based on these findings we divided Group B into two subgroups Subgroup B 1 (VSD of unexpectedly small size) defects less than 0 8 cm per square meter and improved ECG and/or CTR Subgroup B 2 (size of VSD concordant to hemodynamics) defects more than 0 8 cm^2 per square meter (except for 1 case) and unchanged or deteriorated ECG and/or CTR

Fig 4 shows comparison of ECG and CTR changes in an interval of 10 months after catheterization between Subgroups B 1 and B 2 Subgroup B 1 demonstrated ECG evidence of decreasing left ventricular hypertrophy in that the RV_5 and $SV_1 + RV_5$ diminished an average of 12 and 11 mm respectively with almost unchanged

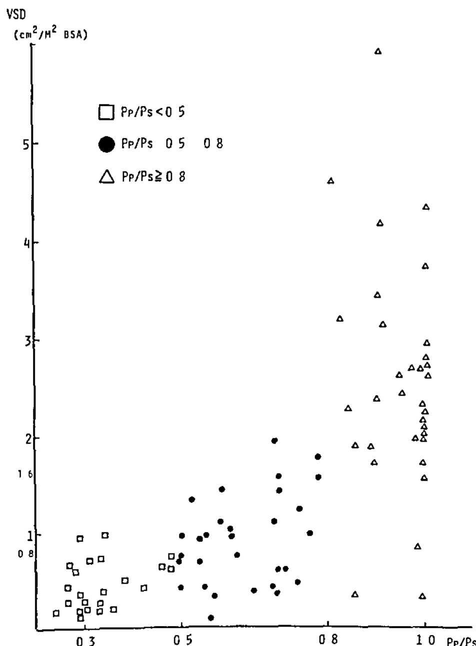


Fig 1 Relationship between Pp/Ps and size of VSD Abbreviations *Pp/Ps* the ratio of systolic pulmonary artery pressure to systolic systemic artery pressure *VSD* ventricular septal defect *BSA* body surface area

tion existed between Pp/Ps and the area of the defect Swan and co workers[17] reported similar findings in 1958

How could one explain the existence of the unexpectedly small VSD in Group B? Since we did not perform cardiac catheterization preoperatively we do not have objective hemodynamic data to help explain this finding but we may be able to indicate three possible causes (1) errors in the measurement of the size of VSD (2) errors in catheterization data and (3) spontaneous decrease in size of VSD

Errors in the measurement of the defect should be considered We presume that those errors were not very critical since the size of the VSD measured at surgery was correlated well with other objective findings such as changes on ECG and cardiac size (Figs 4 and 5 Table III) Measurement was done very carefully by the same surgeon in the same manner

Errors in catheterization or spontaneous decrease in size of VSD In order to explain this hemodynamically strange behavior of VSD size in patients in Group B changes of clinical data in an interval from catheterization to surgery (10 months on the average) were added to the analysis Fig 2 shows relationship between Pp/Ps and VSD size in Group B The size of VSD in all cases

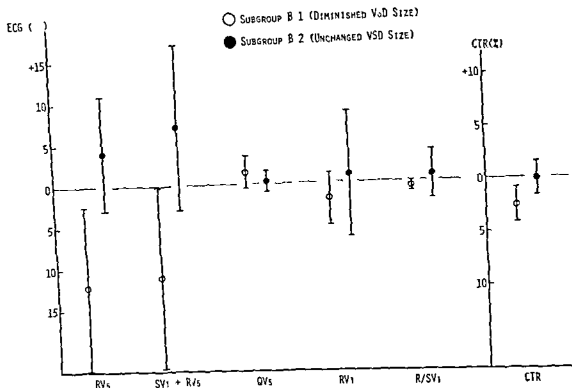


Fig 4 Comparison of ECG and CTR changes between Subgroups B 1 and B 2 in an interval of 10 months after cardiac catheterization Subgroup B 1 demonstrated marked improvement of ECG and CTR Abbreviations *RV_5* R wave in Lead V_5 *SV_1* S wave in Lead V_1 *QV_5* Q wave in Lead V_5 *RV_1* R wave in Lead V_1 *R/SV_1* R/S ratio in Lead V_1 *CTR* cardiothoracic ratio

R/S ratio in Lead V Also CTR of the Subgroup B 1 decreased markedly On the other hand Subgroup B 2 showed ECG evidence of persistence or slight increase of left ventricular hypertrophy with unchanged CTR The differences between them in ECG and CTR were statistically significant ($p < 0.01$) These findings are highly suggestive of the fact that the VSD of Subgroup B 1 indeed decreased in size spontaneously in the 10 month interval between catheterization and surgery and was not an error in catheterization itself

The validity of the catheterization data was tested by correlating it with the ECG and CTR of the time of catheterization among Group A and Subgroups B 1 and B 2 (Fig 5) At the time of diagnostic catheterization there were no differences in ECG and CTR between Subgroups B 1 and B 2 but they were quite different from Group A with $Pp/Ps < 0.5$ RV_1 and CTR in Subgroup B 1 were significantly larger ($p < 0.01$) than in Group A These findings suggest that at the time of catheterization the size of the VSD of Subgroup B 1 was almost the same as the VSD of patients in Subgroup B 2 and much larger than the size of the VSD of Group A

From this we conclude that Subgroup B 1 (42 per cent of patients in Group B with Pp/Ps 0 5 to 0 8) underwent spontaneous decrease in size in the rather short interval of 10 months

In Group C three patients with unexpectedly small sized VSD were found (Fig 1) Two of them operated on at ages 1 year 10 months and 1 year 9 months respectively were found to have very small sized VSD (0 3 and 0 8 cm per square meter) despite the fact that the changes of ECG findings in interval of 7 months from catheterization to surgery were highly suggestive of progression of pulmonary vascular disease (RV_1 30 → 40 mm 26 → 38 mm R/SV_1 1 8 → 3 1 2 0 → 3 2) Postoperative catheterization 2 years after surgery revealed further progression of pulmonary vascular disease These data suggest that in these two patients the VSD was not the primary factor to cause pulmonary vascular disease although we do not know the absolute size of VSD at the time of diagnostic catheterization Another patient was operated on at age 2 years 5

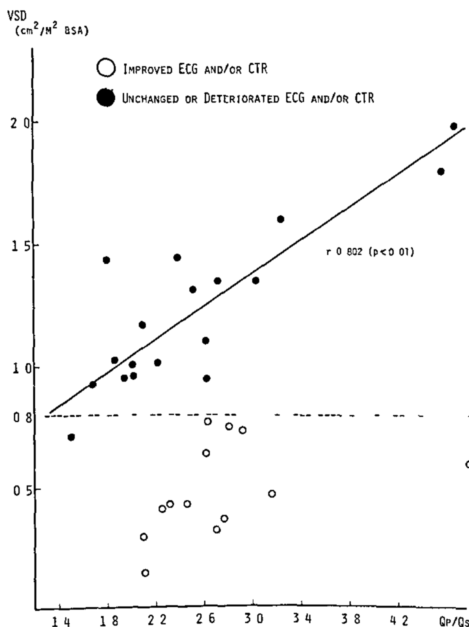


Fig 3 Relationship between Qp/Qs and size of VSD in Group B with Pp/Ps 0 5 to 0 8 Significant correlation exists between Qp/Qs and the size of VSD in the group with unchanged or deteriorated ECG and/or CTR Abbreviations *Qp/Qs* the ratio of pulmonary blood flow to systemic blood flow *CTR* cardiothoracic ratio

Table III ECG and CTR at time of catheterization and surgery (mean ± S D)*

	ECG (mm)						*CTR (%)*	
	Catheterization			*Surgery*			*Catheterization*	*Surgery*
	RV₅	*SV + RV*	*RV*	*RV*	*SV + RV*	*RV*		
Group A	28 ± 9 7	43 8 ± 12 6	9 7 ± 4 5	—	—	—	53 4 ± 3 6	—
Group B								
Subgroup B 1	43 6 ± 10 6	56 1 ± 17 8	15 9 ± 7 9	32 7 ± 10 6	47 1 ± 14 3	14 3 ± 6 7	59 3 ± 4 4	56 1 ± 5 6
Subgroup B 2	44 8 ± 10 2	60 5 ± 18 5	17 2 ± 6 6	49 3 ± 13 3	67 4 ± 23 5	17 8 ± 8 9	61 5 ± 3 6	61 4 ± 3 9
Group C	38 5 ± 14 3	50 1 ± 20 6	20 8 ± 11 2	37 9 ± 11 9	46 4 ± 17 3	21 1 ± 10 3	60 6 ± 3 4	60 7 ± 3 8

ECG electrocardiogram RV R wave in lead V SV S wave in lead V RV R wave in lead V CTR cardiothoracic ratio

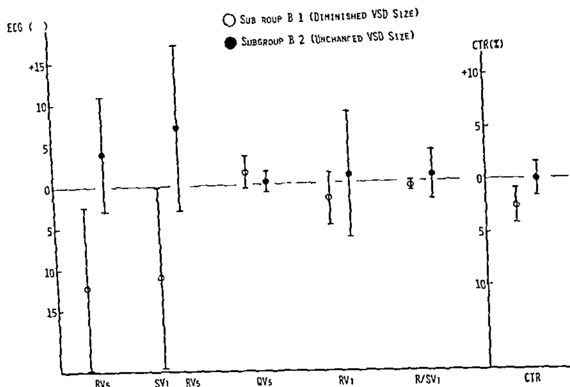


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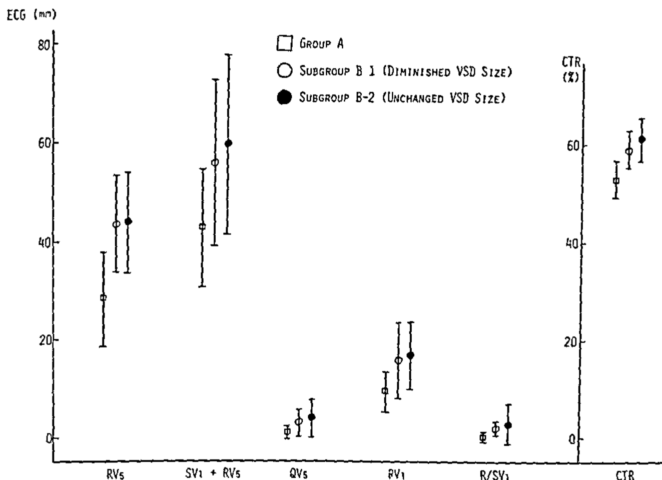


Fig 5 Comparison of ECG and CTR at time of catheterization among Group A Subgroup B 1 and Subgroup B 2 There are no differences in ECG and CTR between Subgroups B 1 and B 2 but they are quite different from Group A For abbreviation see Fig 4

months The ECG findings (biventricular hypertrophy) did not change in the interval from catheterization to surgery, but the VSD was very small (0 3 cm per square meter) It is unknown whether this patient underwent spontaneous decrease in VSD size or not

The size of VSD of another 30 patients (91 per cent of the patients in Group C) was above 1 6 cm per square meter, concordant with hemodynamic principles of VSD The findings of ECG and CTR did not change in the interval from catheterization to surgery (Table III)

Discussion

Our findings indicate that 42 per cent of patients with Pp/Ps 0 5 to 0 8 underwent spontaneous decrease in size of VSD in the very short interval of 10 months Some objections may arise in our inference (1) the lack of measurement of absolute size of VSD at the time of diagnostic catheterization and (2) the lack of recatheterization data just before surgery

The only absolute method to prove spontaneous decrease in VSD size is to measure the size of VSD at time of diagnostic catheterization with surgical exploration In the clinical setup and in a prospective study recatheterization just before surgery should give us a good comparative analysis but although it would have been ideal for practical reasons this could not be repeated

Multiple reports relating size of VSD to hemodynamic data were reviewed and the predictability of such magnitude of the defect was reconfirmed in our study Based on this predictability the comparative analysis of the various clinical findings (ECG CTR) between the time of diagnostic catheterization and just prior to surgery indicate spontaneous decrease in size in the 10 month interval and it was proved at the time of surgery Usefulness of ECG and CTR as a tool in estimating the size of VSD has been well accepted[18] and reconfirmed here

Significantly high incidence of spontaneous decrease in size of VSD has been reported Alcilla and co workers[2] indicated in 1963 that in 70 per cent of their children followed 1 to 7 years the size

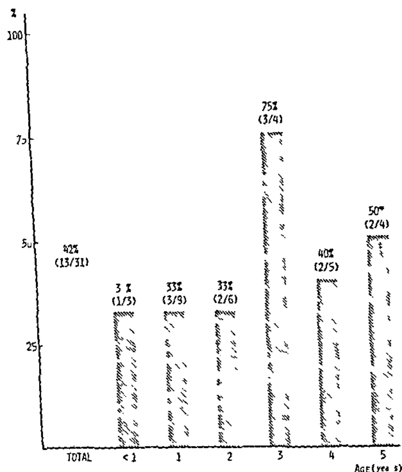


Fig 6 Incidence of decrease in VSD size according to age in Group B with Pp/Ps 0.5 to 0.8

Table IV Clinical predictability of change in VSD size (mean ± S D)

	Diminished VSD size (Subgroup B 1)	Unchanged VSD size (Subgroup B 2)	Statistical analysis
At time of catheterization			
Pp/Ps	0 61 ± 0 08	0 63 ± 0 09	N S
Qp/Qs	[illegible] 6 ± 0 8[illegible]	[illegible] 51 ± 0 84	N S
Rp/Rs	0 17 ± 0 06	0 24 ± 0 09	0 01 < P < 0 05
10 mo after catheterization			
CTR change (%)	−3 1 ± 2 2	0 ± 2[illegible]	P < 0 01
ECG change (mm) RV	−12 4 ± 10 9	+4 1 ± [illegible]5	P < 0 01
SV + RV	−11 1 ± 11.9	+7 1 ± 10 4	P < 0 01

N S not significant.

of VSD diminished and Sandoe reported in 1963 a decrease in size in 50 per cent of cases followed an average of 6 years The follow up period of all these cases was rather long and consequently the time it took for the VSD to decrease in size remains unknown

In our study 42 per cent of cases underwent spontaneous decrease in VSD size in the very short interval of 10 months Moreover the mean size of these diminished VSD was very small averaging 0 5 cm² per square meter If the size of VSD in Subgroup B 1 was the same as that of Subgroup B 2 at the time of catheterization we could state that indeed a great diminution of

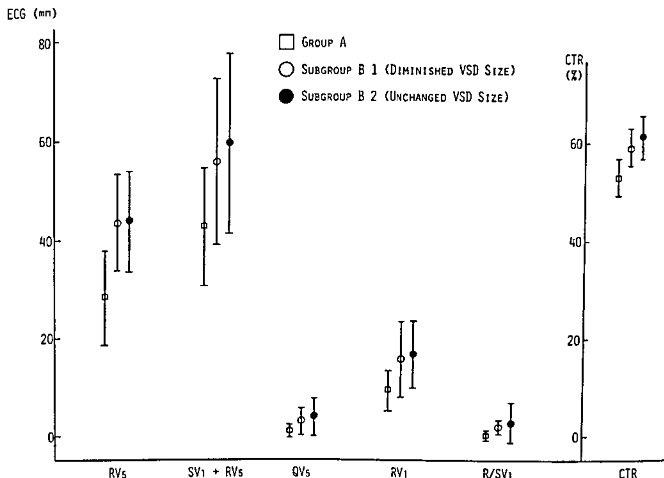


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Significantly high incidence of spontaneous decrease in size of VSD has been reported Arcilla and co workers indicated in 1963 that in 70 per cent of their children followed 1 to 7 years the size

rized Although Pp/Ps and Qp/Qs were not different between two groups Rp/Rs was significantly smaller in the group with the size of the VSD diminished than in the group with the size of the VSD unchanged Thus it appears that Rp/Rs is useful to predict spontaneous decrease in VSD size ECG and CTR were very useful tools to follow the course of the VSD size It is reasonable to observe patients with Pp/Ps 0 5 to 0 8 for 10 to 12 months with serial ECG and CTR determinations If these parameters fail to improve then these patients should be operated on

In patients with Pp/Ps ≧ 0 8 (Group C) three unexpectedly small sized VSD were found Two of them were operated on at the age of 1 year and were catheterized 2 years after operation Postoperative study revealed persistent severe pulmonary hypertension with increasing pulmonary vascular resistance It was thought that the cause of such pulmonary hypertension could be primary or idiopathic in nature If we exclude these two cases from our analysis the incidence of unexpectedly small sized VSD in this particular group with Pp/Ps ≧ 0 8 is only 3 per cent The ECG and CTR of the patients in this group did not change in the 7 month interval Since we did not perform catheterization just before surgery we do not know whether pulmonary vascular disease progressed or not But at least we could say that in patients with Pp/Ps ≧ 0 8 the VSD did not decrease in size in the 7 month interval nor was there clinical evidence of improvement of pulmonary vascular disease

It has been documented that the risk of pulmonary vascular disease in this group is much higher than in Group B with Pp/Ps 0 5 to 0 8 Moreover data concerning long term postoperative pulmonary vascular changes are controversial In the series reported by Cartmill and co workers [?] 57 per cent showed diminution of pulmonary resistance ratios On the other hand Friedli and co workers reported in 1974 that patients with Rp/Rs > 0 33 who were operated on after the age of 2 years most often showed progressive pulmonary vascular disease subsequently These reports and our findings indicate that patients with Pp/Ps ≧ 0 8 should have surgery without delay

Summary

Eighty seven patients with isolated ventricular septal defect (VSD) operated on in the first 5 years of life that had a mean interval of 10 months between diagnostic catheterization and surgery were studied retrospectively The size of the VSD was correlated with diagnostic catheterization data and comparative analysis of clinical findings (ECG and CTR) was made between the time of diagnostic catheterization and just prior to surgery The study showed that 42 per cent of patients with the ratio of systolic pulmonary artery pressure to systolic systemic artery pressure (Pp/Ps) 0 5 to 0 8 had a marked reduction in size of VSD in a rather short interval of 10 months In patients with Pp/Ps ≧ 0 8 the incidence of decrease in VSD size was close to nil The highest incidence of decrease in VSD size was seen in patients with high flow and low resistance ECG and CTR were very useful diagnostic tools to follow the course of the VSD size

The patients with Pp/Ps 0 5 to 0 8 should be observed for an interval of 10 to 12 months expecting spontaneous decrease in VSD size If clinical parameters (ECG CTR) fail to improve in that interval then the patients should have surgery The patients with Pp/Ps ≧ 0 8 should be operated on without delay

REFERENCES

1 Bloomfield D K The natural history of ventricular septal defect in patients surviving infancy Circulation 29 914 1964
2 Arcilla R A, Agustsson M H Bicoff J P Lynfield J, Weinberg M Fell E H, and Gasul B M Further observations of the natural history of isolated ventricular septal defects in infancy and childhood Serial cardiac catheterization studies in [?]5 patients Circulation 28 560 1963
3 Hoffman J I E and Rudolph A M The natural history of ventricular septal defects in infancy Am J Cardiol 16 634 1965
4 Sandoe F Congenital isolated ventricular septal defect Hemodynamics clinical features and prognosis after the age of ? years, Thesis Copenhagen 1963 Ejnar Munksgaard Forlag p 1[?]
5 Nadas A S Scott L W, Haudk A J and Rudolph A M Spontaneous functional closure of ventricular septal defects, N Engl J Med 264 309 1961
6 Evans J R Rowe R D and Keith J D Spontaneous closure of ventricular septal defects Circulation 22 1044 1960
7 Kaplan S Daoud G I Benzing G III Devine F J Glass I H and McGuire J Natural history of ventricular septal defect Am J Dis Child 105 581 1963
8 Nadas A S and Fyler D C Ventricular septal defect A review of current thoughts, Arch Dis Child 43 68 1968
9 Keith J D Rose V Collins G and Kidd B S L Ventricular septal defect Incidence morbidity and mortality in various age groups Br Heart J 33(Suppl.) 81 1971
10 Ritter D C Feldt R H Weidman W H and DuShane J W Ventricular septal defect Circulation 32(Suppl 3) 42 1965
11 Hoffman J I E and Rudolph A M Pulmonary vascular resistance and ventricular septal defect Pediatrics 38 220 1966

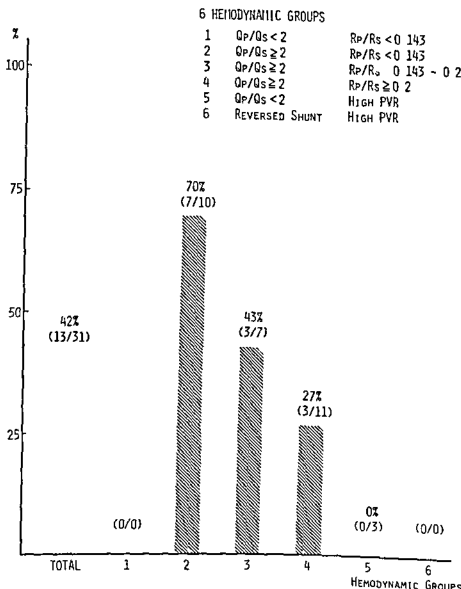


Fig 7 Incidence of decrease in VSD size according to six hemodynamic groups in Group B with Pp/Ps 0 5 to 0 8 Strong correlation exists between them The incidence of decrease in VSD size in hemodynamic Group 2 is very high at 70 per cent Abbreviation *PVR* pulmonary vascular resistance Quoted from Kidd s original in 1965

VSD size (1 2 → 0 5 cm per square meter) occurred in this short interval According to our data and other reports[1 3 10] VSD of this size does not require surgery To be able to postpone surgical intervention safely and expect a spontaneous decrease in size of VSD the incidence of pulmonary vascular disease and the period in which pulmonary vascular disease would develop should be established The incidence of pulmonary vascular disease in patients with Pp/Ps 0 5 to 0 8 has not been established but probably it is not high enough to hasten surgical treatment routinely[1 3 11] The time required to develop pulmonary vascular disease remains unknown

In order to postpone surgery safely it would be useful to be able to predict which VSD will decrease in size spontaneously Fig 6 correlates incidence of decrease in size of VSD and age

Although many reports[1 6] indicate that the occurrence of spontaneous decrease in size of VSD is higher as the ages decrease our study fails to demonstrate such correlation Fig 7 summarizes the incidence of decrease in VSD size in relation to Kidd s and co workers[1] six hemodynamic groups Strong correlation between hemodynamic group and the incidence of decrease in VSD size was found that is the incidence of decrease in VSD size was 70 per cent in hemodynamic group 2, 43 per cent in hemodynamic group 3 27 per cent in hemodynamic group 4 and 0 per cent in hemodynamic group 5 This means that the VSD with high flow and low resistance has a higher tendency to decrease in size spontaneously

In Table IV the clinical parameters to predict spontaneous decrease in VSD size are summa

Experimental and laboratory reports

Experimental study of myocardial infarction through the use of body surface isopotential maps Ligation of the anterior descending branch of the left coronary artery

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Masatoshi Wada M D
Junichi Sugenoya M D
Hideaki Toyoshima M D
Junji Toyama M D
Kazuo Yamada M D
Nagoya Japan

The body surface isopotential map (referred to below as map for short) which is produced by electrocardiographic (ECG) recording from a large number of lead points on the body surface has served as a method to examine the electrical phenomena of the heart [3] Of late years since Taccardi first gained a sequence of maps in men and dogs all through ventricular depolarization it has become clear that the distribution of positive and negative potentials and the location of maximum and minimum in each map have a close relation with the ventricular activation process although the system for recording and displaying isopotential maps was too complicated to be widespread

This difficulty is however becoming less significant with the use of computers to process the large amounts of body surface ECG data In other words the development of the computer has made the mapping system much easier and consequently the study of this field has greatly progressed Obviously maps contain important diagnostic information that is *not* available in conventional FCG s and vectorcardiograms Therefore clinical application of maps may be expected much more in the future in order to diagnose various cardiac diseases

This report will investigate whether or not diagnostic accuracy can be achieved from maps in differentiating the location and extent of myocardial infarction which was caused experimentally by ligation of the orifice or branch of the left anterior descending coronary artery

Method

Coronary artery occlusion Eleven mongrel dogs weighing from 8 to 12 kilograms were anesthetized with intraperitoneal thiamylal sodium (20 mg per kilogram) and maintained by artificial respiration Then the chest of each dog was opened by an incision at the left fifth intercostal space and myocardial infarction was caused by ligation of the orifice or branch of the left anterior descending coronary artery In 1 to 5 weeks after ligation each heart was isolated and cut perpendicular to the long axis of the left ventricle into slices 1 to 2 cm thick to observe directly the extent and location of infarction The extent and location were also confirmed by hematoxylin and eosin staining

Record and display of maps As the procedure for record and display of maps has been reported previously[1] [13] in detail it will be explained only briefly in this paper Each map was based on the record of the unipolar lead ECG s obtained through the use of needle electrodes attached to

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12 Collins G Calder L and Rose V Ventricular septal defect Clinical and hemodynamic changes in the first five years of life *Am Heart J 84 695 1972*

13 DuShane J W Weidman W H and Ritter D G Influence of the natural history of large ventricular septal defects on management of patients Birth Defects **8** 63 1972

14 Savard M Swan H J C Kirklin J W and Wood E H Hemodynamic alterations associated with ventricular septal defect *in* Bass A D and Moe G K editors Symposium on congenital heart disease Washington D C 1960 American Association for the Advancement of Science p 141

15 Lynfield J Gasul B M Arcilla R and Luan L L The natural history of ventricular septal defects in infancy and childhood Based on serial cardiac catheterization studies Am J Med **30** 357 1961

16 Lucas R V Jr Adams P Jr Anderson R C Meyne N G Lillehei C W and Varco R L The natural history of isolated ventricular septal defect A serial physiologic study Circulation **24** 1372 1961

17 Swan H J C Savard R M and Kirklin J W Relation of size of ventricular septal defects to circulatory dynamics J Clin Invest **37** 934 1958

18 DuShane J W Weidman W H Brandenburg R O and Kirklin J W The electrocardiogram in children with ventricular septal defect and severe pulmonary hypertension Correlation with response of pulmonary arterial pressure to surgical repair Circulation **22** 49 1960

19 Vince D J and Keith J D The electrocardiogram in ventricular septal defect Circulation **23** 225 1961

20 Keith J D Rowe R D and Vlad P Heart disease in infancy and childhood Ed 2 New York 1967 The Macmillan Company

21 Kidd L Rose V Collins G and Keith J The hemodynamics in ventricular septal defect in childhood Am Heart J **70** 732 1965

22 Cartmill T B DuShane J W McGoon D C and Kirklin J W Results of repair of ventricular septal defect J Thorac Cardiovasc Surg **52** 486 1966

23 Friedli B Kidd B S L Mustard W T and Keith J D *Ventricular septal defect with increased pulmonary vascular resistance* Am J Cardiol **33** 403 1974

24 Hallidie Smith K A Hollman A Cleland W P Bentall H H and Goodwin J F Effects of surgical closure of ventricular septal defects upon pulmonary vascular disease Br Heart J **31** 246 1969

25 Castaneda A R Zamora R and Nicoloff D M High pressure high resistance ventricular septal defect Ann Thorac Surg **12** 29 1971

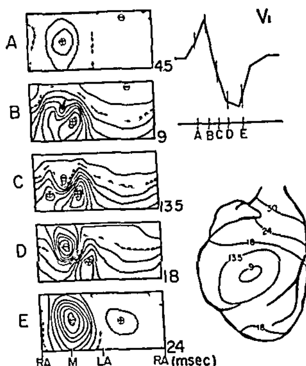


Fig 2 Five maps showing a typical sequence of ventricular activation in control for the duration of QRS from 4 5 (*A*) to 24 msec (*E*) respectively correspond to the instants recorded from the QRS complex of the Lead V ECG shown in the right upper inset The broken line indicates the equipotential line of Wilson s central terminal (zero line) The shaded area indicates the positive zone where the potential is higher than zero The white area indicates the negative zone where the potential is lower than zero (+) indicates a maximum and (−) a minimum the arrow (map *B*) indicates the pseudopod like irregularity of the equipotential lines. *RA* Right mid axillary line *M* mid-sternal line *LA* left midaxillary line The epicardial activation sequence is also illustrated in the cardiac schema in the right lower corner The figures on each isochronic line indicate the time (msec) after the onset of the ventricular depolarization The breakthrough of the activation front to the epicardium is first recognized at 9 msec

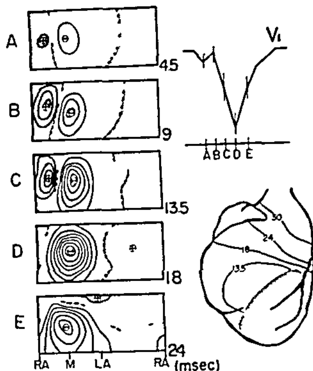


Fig 3 Typical Group A maps The epicardial sequence is also illustrated in the cardiac schema in the right lower corner The vertical shading indicates the area of QS complexes observed in the epicardial lead

Results

Evaluation for possible artifact induced by surgical open chest operation As it is necessary to examine whether the incision of the chest has any influence or not on the map three dogs were used to see the difference between before and after the incision of chest The results were as follows (1) The maximum difference in the absolute value of potential from each lead point was below 0 8 mV all through ventricular activation (2) The rate of voltage difference between pre and postoperation was under 25 per cent (3) There was no distinctive difference in the distribution of positive and negative areas and the running of the zero line

Therefore it can be thought that the operation had no significant effect on the map

Control map With some small differences all normal dogs had rather similar map patterns So the typical maps from 4.5 to 24 msec were taken as an instance of control as shown in Fig 2

To illustrate the body surface isopotential map the map was cut and separated along the right midaxillary line on the thoracic surface and was fanned and spread open

The shaded area illustrates the positive zone the white area the negative zone each solid line illustrates an equipotential line drawn at an interval of 0 4 mV and the broken line illustrates the potentials of Wilson s central terminal which may be called the zero line The (+) indicates maximum and (−) minimum

The QRS complex of Lead V_1 ECG is shown at the right upper corner of each figure expressing the serial maps Letters put to the left of

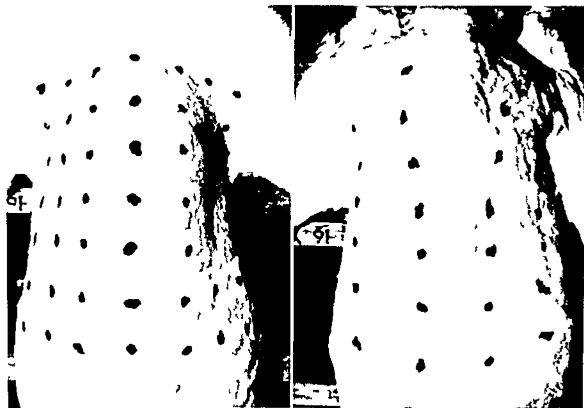


Fig 1 Black spots shown on the anterior (left) and posterior (right) thoracic surface represent the lead points for the unipolar lead ECG s

85 lead points on each dog's chest surface (59 on the anterior, and 26 on the dorsal) (Fig 1) in a supine position under anesthesia and artificial respiration

The unipolar lead ECG s were recorded at a time from each two lead points of the dog s surface onto the magnetic tape (Teac Corpora tion, 1/4 DT 250 1800 PR) through the use of a three channel data recorder (Teac Corporation R 100) together with a fixed lead as time reference This procedure was repeated 43 times until all the 85 unipolar lead ECG's were recorded

The 85 unipolar lead ECG s recorded onto the magnetic tape were reproduced, transmitted to an A/D converter, and treated by the mapping system with a minicomputer (JEC 5 Type Nihon Denshi Co , Ltd) Sampling rate was about 2,600 samples per second for each lead Synchroniza tion of 43 pairs of unipolar lead ECG's was performed by using the steepest point of down ward deflection of the time reference ECG The Wilson central terminal potential was taken as zero Thus a body surface isopotential map was obtained every 1 5 msec throughout the entire time course of the ventricular depolarization

All the dogs had two series of maps recorded before and after (a week later) experimental myocardial infarction In one case, maps were obtained not only 1 week after but also 4 weeks after the ligation No difference of map pattern between 1 and 4 weeks after could be observed

Epicardial sequence of the ventricular depolar ization The arrival time of the activation at the epicardial surface was obtained in all 11 cases of infarction

The procedure used to measure the arrival time accurately is briefly described below for a detailed description see Toyoshima [11] The direct unipolar and simultaneous bipolar lead ECG's were recorded from 30 to 40 points on the epicar dium at speeds of 20 cm per second through the use of direct writing electromagnetic oscillograph together with the same time reference ECG

The delineation of the isochronic map express ing the epicardial sequence of the ventricular depolarization of the canine heart was obtained by plotting the points showing the same arrival time of the activation at the epicardial surface

The epicardial sequence of the ventricular depolarization was obtained from three healthy dogs after maps had been recorded for control

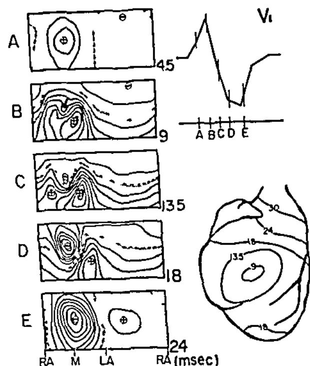


Fig 2 Five maps showing a typical sequence of ventricular activation in control for the duration of QRS from 4 5 (*A*) to 24 msec. (*E*) respectively correspond to the instants recorded from the QRS complex of the Lead V ECG shown in the right upper inset The broken line indicates the equipotential line of Wilson s central terminal (zero line) The shaded area indicates the positive zone where the potential is higher than zero The white area indicates the negative zone where the potential is lower than zero (+) indicates a maximum and (–) a minimum the arrow (map *B*) indicates the pseudopod like irregularity of the equipotential lines, *RA* Right mid axillary line *M* mid-sternal line *LA* left midaxillary line The epicardial activation sequence is also illustrated in the cardiac schema in the right lower corner The figures on each isochronic line indicate the time (msec) after the onset of the ventricular depolarization The breakthrough of the activation front to the epicardium is first recognized at 9 msec

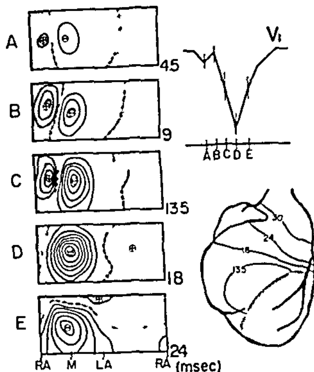


Fig 3 Typical Group A maps The epicardial sequence is also illustrated in the cardiac schema in the right lower corner The vertical shading indicates the area of QS complexes observed in the epicardial lead

Results

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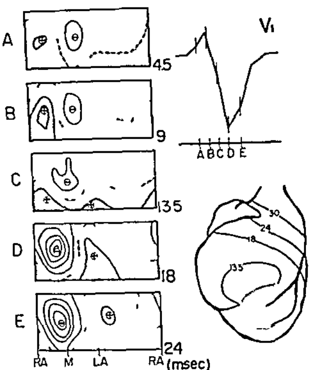


Fig 5 Typical Group B maps. The epicardial sequence is also illustrated in the cardiac schema in the right lower corner The vertical shading indicates the area of QS complexes observed in the epicardial lead

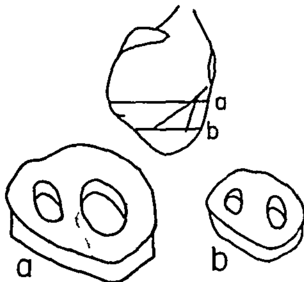


Fig 6 Cross-sections a b illustrate the location and extent of infarction in the case of Fig 5

During 9 to 13 5 msec the entire left anterior surface was still negative and the map pattern remained almost unchanged

At 18 msec the negative area enlarged and occupied the whole anterior chest surface There were no positive potentials on the left anterior or on the left axillary the minimum maintained its position but the maximum moved toward the dorsal region

At 24 msec the negative area occupied the whole anterior chest surface the positive the dorsal surface The map at this instant was similar to that of control Thereafter there was little difference in map pattern between control and Group A The characteristics of Group A were as follows (1) The negative potentials always occupied the left anterior chest surface (including the left axillary region) for the entire duration of the ventricular activation (2) A large part of the dorsal region was occupied by the positive potentials from the early stage (3) There was no appearance of the maximum on the left anterior chest surface (including the left axillary region) (4) The minimum was always observed near the center of the anterior chest surface all through the period of ventricular activation

Group B (4 cases) Typical maps are shown in Fig 5 The epicardial activation sequence is also illustrated in the cardiac schema in the right lower corner of Fig 5 The vertical shading indicates the area of QS complexes observed in the epicardial unipolar lead The location and extent of infarction are illustrated in the cardiac schema of Fig 6

At 4 5 msec like Group A the left anterior chest surface was covered by the negative area which unlike Group A did not expand into the right anterior surface across the midsternal line The positive occupied the whole right anterior surface but did not spread into the entire dorsal region a minimum was present a little on the left side of the central part of the anterior During 9 to 13 5 msec the positive area expanded into the lower region of the left anterior chest surface There appeared a maximum on the left anterior chest surface The minimum moved a little to the right and was located near the center of the anterior

At 18 msec the left axillary surface became positive The extent of positive potentials at this instant was smaller than that of control The positions of the maximum and the minimum were similar to those of control

At 24 msec the map pattern was similar to that

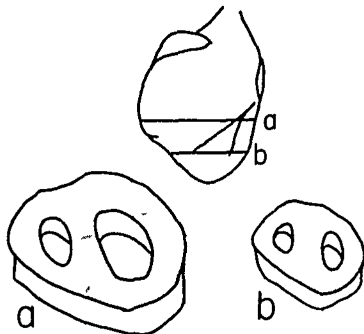


Fig 4 The location and extent of infarction in case of Fig 3 is shown by cross sections taken at *a* *b* The shaded area indicates infarcted area

respective maps correspond to ones written under the QRS complex of Lead V_1 and indicate the instants at which the maps were obtained Figures to the right of the respective map indicate the time interval from the onset of the QRS complex to the respective instants

The epicardial activation sequence is also illustrated in the cardiac schema in the right lower corner of Fig 2

At 4 5 msec from the onset of ventricular activation, the positive potentials occupied the anterior chest surface and the negative the dorsal surface A single maximum was present near the center of the anterior chest surface and a minimum on the dorsal

At 9 msec the positive potentials still covered the anterior chest surface and had expanded further into the lower dorsal region The maximum and minimum hardly changed their positions However there appeared a potential sink in the positive area as indicated by the arrow in the map, accompanied by the irregularity of equipotential lines like a pseudpod (This pseud pod like irregularity was observed in every case of control map between 9 to 13 5 msec after the onset of ventricular depolarization) This irregu larity may be said to be closely connected with the breakthrough of the electrical wave front to the epicardium

At 13 5 msec the potentials of the pseudpod like region became still lower and formed a negative area, which displayed a wedge shape in the positive area With this change, the maximum divided into two separate maxima, a major maximum on the left anterior surface and a minor maximum on the right

At 18 msec the negative area of the anterior chest surface was more enlarged The minimum which had already existed near the center of the anterior surface remained unchanged mean while the minor maximum disappeared at this instant and the major maximum decreased in its potential and moved a little to the left side

At 24 msec the whole anterior chest surface became negative and the dorsal region positive The maximum moved from the left anterior chest surface to the dorsal The minimum maintained its central position Thereafter the potentials had a tendency to lower themselves but the pattern remained unaltered until the end of ventricular activation

Myocardial infarction The dogs with experi mental myocardial infarction were classified into three groups according to the location and extent of infarction Group A over half of the ventric ular septum and the larger part of the left anterior and left lateral wall were infarcted Group B the ventricular septum the left anterior wall and the left lateral wall were partly infarcted Group C the left anterior wall and the left lateral wall were infarcted and the ventric ular septum was almost normal

Each group had its own characteristic maps which are given as a typical instance of each group in the following paragraphs

Group A (4 cases) Typical maps are shown in Fig 3 The epicardial activation sequence is also illustrated in the cardiac schema in the right lower corner of Fig 3 The vertical shading indi cates the area of QS complexes observed in the epicardial unipolar lead The location and extent of infarction are illustrated in the cardiac schema of Fig 4

At 4 5 msec the map was different from that of control The positive area did not cover the whole anterior chest surface but the negative area occupied the left anterior chest surface and a part of the right anterior chest surface across the midsternal line There existed a minimum near the central position of the anterior region

pared the electrical information obtained from the heart with that on the body surface and suggested that maps were valuable in the diagnosis of myocardial infarction

This study was designed to evaluate the location and extent of myocardial infarction obtained through the use of body surface isopotential maps which represent the ventricular activation process well enough Infarction is believed to cause changes of map pattern by reason that the infarcted region is electrically inert and fails to activate The following discussion is based on serial inspection of the ventricular activation process

According to the studies of Scher and Young [8, 9] the study of Boineau and associates [6] and the electrical information we obtained from the epicardial surface shown in Figs 2 3 5 and 7 at 4 5 msec after the onset of ventricular activation the activation front mainly spreads ventrally from the ventricular septum and also spreads outward from the left and right cavity toward the left and right anterior area Therefore in the map reflecting the ventricular activation at this instant the positive area covers nearly the whole anterior chest surface and the negative the dorsal A maximum is present near the central position of the anterior chest surface and a minimum on the upper dorsal surface (Fig 2 *A*)

In Group A however the septal and left ventricular anterior wall is infarcted and consequently a lack of electromotive force in the infarcted region occurs though there is some activity spreading only in the right ventricular anterior wall which is directed ventrally Therefore in the map the negative area occupies the left anterior chest surface and a part of the right anterior chest surface Meanwhile at this instant there is an appearance of the electromotive force progressing dorsally which is canceled in the control map by electromotive force progressing ventrally Therefore the positive potentials cover most of the dorsal region in the map (Fig 3 *A*)

In Group B as compared with Group A the extent of infarction is smaller and more cardiac muscle remains That is impairment of electromotive force progressing forward is less than in Group A Accordingly in the map the negative area is present only on the left anterior surface and a part of the dorsal region becomes positive In addition both the maximum and the minimum in Group B are located a little to the left side compared with Group A (Fig 5 *A*)

In Group C as the septal and adjacent anterior wall is kept intact the distribution of the positive and negative areas and the location of maximum and minimum are similar to those in control though the positive area on the left anterior surface is a little smaller (Fig 7 *A*)

During 9 to 13 5 msec in control there occurs a breakthrough of the electrical wave front to the epicardium of the right ventricular free wall Consequently the activation front breaks into two one propagating toward the left anterior ventricular wall and the other the right free wall Therefore in the map at this instant the negative area wedges itself into the positive area (Fig 2 *B C*) In Group A however the larger part of the left ventricular wall is infarcted and cannot depolarize In the map therefore the negative area continues to occupy the left anterior chest surface (Fig 3 *B C*)

Meanwhile in Group B a part of the left anterior chest surface becomes positive a maximum appearing on the left anterior chest surface because the infarcted region of the left ventricular wall is not so large as in Group A and there is some activity of residual cardiac muscle in the left anterior wall (Fig 5 *B C*)

In Group C for the first time at this period a change appears in the map The left anterior chest surface which is positive in control during this phase of ventricular activation is occupied by the negative potentials because of the infarction of the left ventricular anterior and lateral wall (Fig 7 *B C*)

At 18 msec in control activity predominates the left lateral and posterior wall Therefore the positive potentials cover the dorsal region and the negative potentials enlarge and cover most of the anterior chest (Fig 2 *D*)

In Group A most of the lateral wall is infarcted and cannot make an activation front Consequently even at this period the left anterior chest surface remains negative and a maximum is present on the dorsal (Fig 3 *D*)

In Group B the distribution of positive and negative areas and the location of the maximum and minimum resemble those in control (Fig 5 *D*) The reason is hypothesized to be that the larger part of lateral wall is free from infarction and has normal depolarization

In Group C one case was similar to that of

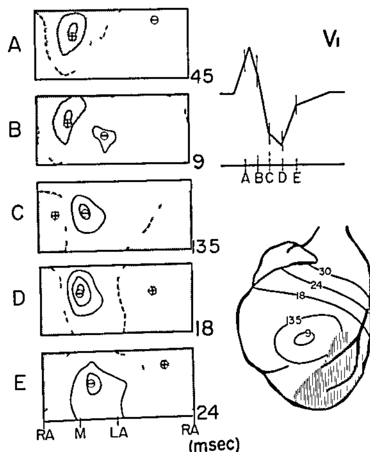


Fig 7 Typical Group C maps The epicardial sequence is also illustrated in the cardiac schema in the right lower corner The vertical shading indicates the area of QS complexes observed in the epicardial lead

of control and thereafter it did not break the similarity The characteristics of Group B were as follows (1) At 4 5 msec as in the case of Group A the negative potentials covered the left anterior chest surface but on and after 9 msec the positive area spread into a lower part of the left anterior surface (2) In the early stages of ventricular activation a part of the dorsal chest surface became positive (3) A maximum appeared on the left anterior chest surface (including the left axillary region) (4) In the early stage a minimum was present on the anterior chest surface but its location was a little to the left compared with the one in Group A

Group C (3 cases) Typical maps are shown in Fig 7 The epicardial activation sequence is also illustrated in the cardiac schema in the right lower corner of Fig 7 The vertical shading indicates the area of QS complexes observed in the epicardial unipolar lead The location and extent of infarction are illustrated in the cardiac schema of Fig 8

At 4 5 msec the positive area on the left

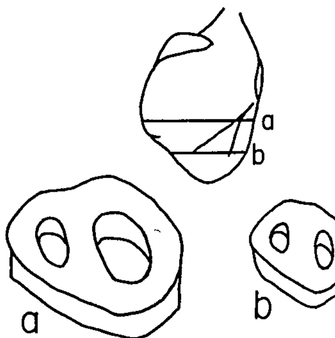


Fig 8 Cross sections illustrate the location and extent infarction in the case of Fig 7

anterior chest surface was a little smaller th that of control, though the distribution of posit and negative areas was similar to those control

At 9 msec the negative potentials appeared the left anterior chest surface and the minim also turned up on the left anterior region

At 13 5 msec the greater part of the l anterior chest surface was covered by the ne tive potentials The minimum was present n the center of the anterior chest surface

At 18 msec the anterior chest surface beca negative and the dorsal positive The maxim moved to the dorsal surface

At 24 msec there was no distinctive differe between pre and postinfarction in the distri tion of the positive and negative potentials a the location of the maximum and minimum

The characteristics of group C were analyzed follows (1) At 4 5 msec the whole anterior ch surface was occupied by the positive potenti (2) At 9 msec, however the negative potenti appeared on the left anterior chest surface The minimum first appeared on the dorsal a moved to the left anterior and finally to t center of the anterior chest surface

Discussion

Boineau and associates[15] reported the relatio ship of body surface potentials and ventricu excitation in myocardial infarction They co

pared the electrical information obtained from the heart with that on the body surface and suggested that maps were valuable in the diag nosis of myocardial infarction

This study was designed to evaluate the loca tion and extent of myocardial infarction obtained through the use of body surface isopotential maps which represent the ventricular activation pro cess well enough Infarction is believed to cause changes of map pattern by reason that the infarcted region is electrically inert and fails to activate The following discussion is based on serial inspection of the ventricular activation process

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In Group B as compared with Group A the extent of infarction is smaller and more cardiac muscle remains That is impairment of electro motive force progressing forward is less than in Group A Accordingly in the map the negative area is present only on the left anterior surface and a part of the dorsal region becomes positive In addition both the maximum and the minimum in Group B are located a little to the left side compared with Group A (Fig 5 *A*)

In Group C as the septal and adjacent anterior wall is kept intact the distribution of the positive and negative areas and the location of maximum and minimum are similar to those in control though the positive area on the left anterior surface is a little smaller (Fig 7 *A*)

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At 18 msec in control activity predominates the left lateral and posterior wall Therefore the positive potentials cover the dorsal region and the negative potentials enlarge and cover most of the anterior chest (Fig 2 *D*)

In Group A most of the lateral wall is infarcted and cannot make an activation front Consequently even at this period the left ante rior chest surface remains negative and a maximum is present on the dorsal (Fig 3 *D*)

In Group B the distribution of positive and negative areas and the location of the maximum and minimum resemble those in control (Fig 5 *D*) The reason is hypothesized to be that the larger part of lateral wall is free from infarction and has normal depolarization

In Group C one case was similar to that of

Group A, and two cases to Group B, because the former and latter infarctions resemble those of Groups A and B, respectively That is, no characteristics of Group C may be observed at this stage (Fig 7, *D*)

At 24 msec the activation wave front mainly spreads toward the ventricular posterior wall As a result the anterior chest surface becomes negative and the dorsal positive At this instant, all groups form normal activation fronts on the posterior wall, so that the map pattern is similar to that of control (Figs 2 3 5 7, *E*)

Thus it has been shown that each group of myocardial infarction displays its own characteristic maps

It can be deduced from this experiment that the areas where QS complexes are observed in epicardial unipolar lead are projected onto the body surface and that the extent of the QS areas closely connected with the extent of the negative area and the location of the minimum in the maps That is, the maps reflect well the degree of the absence of electromotive force caused by infarction

McLaughlin and associates[19] reported that the characteristic map pattern was obtained in cases of anteroseptal infarction and posterior infarction They also said that the difference map (between pre and postinfarction) was very useful to diagnose the infarction accurately However, as they indicated, the difference map is very difficult to obtain in clinical cases

But it can be said that the differences in extent and location of infarction on the scale of the data presented in this paper can be deduced through the postinfarction maps alone throughout the entire course of ventricular depolarization

Clinically, Young and Lawrie [0] also suggested that maps obtained from myocardial infarction patients varied according to the difference in the location of the infarction

Therefore it can be said that the use of the sequential maps obtained through the ventricular activation process makes it possible to diagnose the location and extent of myocardial infarction

Summary

This investigation was undertaken to diagnose the location and extent of myocardial infarction with the use of maps which give significant information about the ventricular activation process

Myocardial infarction was experimentally caused by ligation of the anterior descending branch of the left coronary artery

All cases were classified into three groups (A, B and C) according to the location and extent of infarction The map of each group had its own characteristics, as follows

In Group A no positive potentials appeared on the left anterior chest surface all through ventricular depolarization In Group B, like Group A the negative area occupied the whole left anterior chest surface in the early stage But in the later stages there appeared a positive area on the left anterior surface As to Group C, there was no abnormality in its early stage but in its middle stage, the negative area was found on the left anterior chest surface

Thus the sequential maps can be helpful in diagnosing the location and extent of myocardial infarction and will be applied to clinical use much more

We would like to express our appreciation to Mr John Haig of the Language Center Nagoya University for reading previous drafts of this paper and giving us numerous suggestions concerning language and style And we also thank to Miss M Taki for her kind translation advices

REFERENCES

1 Nahum L H Mauro A Chernoff H M and Sikand R S Instantaneous equipotential distribution on surface of the human body for various instants in the cardiac cycle J Appl Physiol 3 454 1951
2 Mauro A Nahum L H Sikand R S and Chernoff H M Equipotential distribution for the various instants of the cardiac cycle on the body surface of the dog Am J Physiol 168 584 1952
3 Sikand R S Mauro A and Nahum L H Instantaneous distribution of the electrocardiographic potential on the body surface of the normal man during the T interval J Appl Physiol 4 916 1952
4 Taccardi B Distribution of heart potentials on the thoracic surface of normal human subjects Circ Res 12 341 1963
5 Taccardi B Distribution of heart potentials on dogs thoracic surface Circ Res 11 862 1962
6 Spach M S Silberberg W P Boineau J P Barr R C Long G C Gallie T M Cabor J B and Wallace A G Body surface isopotential maps in normal children ages 4 to 14 years AM HEART J 72 640 1966
7 Blumenschein S D Spach M S Boineau J P Barr R C Gallie T M Wallace A G and Ebert P A Genesis of body surface potentials in varying types of right ventricular hypertrophy Circulation 38 917 1968
8 Taccardi B De Ambroggi L and Domenico R Chest maps of heart potentials in right bundle branch block J Electrocardiol 2 109 1969

9 Karsh R B Spach M S and Barr R C Interpretation of isopotential surface maps in patients with ostium primum and secundum atrial defects, Circulation 41 913 19 0
10 Olliff B C Horan L G and Flowers N C Correlative analysis of vectorcardiograms and serial instantaneous surface maps in normal young men Am Heart J 83 780 1972.
11 Flowers N C and Horan L G Comparative surface potential patterns in obstructive and nonobstructive cardiomyopathy Am Heart J 86 196 1973
12 Yamada K Toyama J Wada M Sugiyama S Sugenoya J Toyoshima H Mizuno Y Sotohata I Kobayashi T., and Okajima M Body surface isopotential mapping in Wolff Parkinson White syndrome—noninvasive method to determine the localization of the accessory atrioventricular pathway Am Heart J 90 721 1975
13 Yamada K Toyama J Toyoshima H Wada M and Sugiyama S Body surface isopotential maps of experimental myocardial infarction Annual report of Research Institute of Environmental Medicine Nagoya Univ 26 78 19 5 (in Japanese)
14 Toyoshima H Correlations between the spread of ventricular activation and map patterns of measured and difference maps Am Heart J 92 183 19 6
15 Boineau J P., Spach, M S., Sabiston D C., Blumenschein S D Gallie T M and Long F C Body surface potentials and ventricular excitation in myocardial infarction Manning G W., and Ahuja S P., editors Electrical activity of the heart Springfield Ill., 1969 Charles C Thomas, Publisher p 83
16 Scher A M., and Young A C The pathway of ventricular depolarization in the dog, Circ Res 4 461 1956
17 Scher A M and Young A C Ventricular depolarization and the genesis of QRS Ann N Y Acad Sci 65 768 1957
18 Boineau J P Spach, M S., Pilkington T C., and Barr R C Relationship between body surface potential and ventricular excitation in the dog, Circ Res. 19 489 1966
19 McLaughlin V W Flowers N C., Horan L G., and Killam H A W Surface potential contribution from discrete elements of ventricular wall Am J Cardiol 34 302 19 4
20 Young B D., and Lawrie T D V Body surface mapping in myocardial infarction. *Proceedings of the satellite symposium of the 25th international congress of physiological sciences the electrical field of the heart* 333 Presses Academiques Européennes, Bruxelles, 1972.

Effects of vagal stimulation, atropine, and propranolol on fibrillation threshold of normal and ischemic ventricles

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Ventricular fibrillation is one of the major causes of death in patients with acute myocardial infarction Ventricular premature beats are the most common arrhythmia observed during myocardial infarction and are a precursor of ventricular tachycardia and fibrillation The initiation and maintenance of ventricular arrhythmias are thought to be due to either a re entrant mechanism or abnormal pacemaker activity [1] It has been also suggested that the autonomic nervous system plays a significant role in the induction of ventricular arrhythmias For example sympathetic stimulation facilitates the development of ventricular arrhythmias,[2,3] whereas sympathectomy or β adrenergic blockade decreases the incidence of ventricular arrhythmias during experimental myocardial infarction [4,5]

Recent studies have shown that increased vagal tone may decrease the probability of ventricular arrhythmias during experimental myocardial infarction It has been shown that vagal stimulation decreases the incidence of ventricular arrhythmias and decreases ventricular vulnerability to fibrillation during acute coronary occlusion [6,7] Administration of atropine has been shown to increase the incidence of ventricular arrhythmias during coronary occlusion [7] These results led to the conclusion that atropine may actually increase the risk of ventricular arrhythmias and vagotonic drugs may provide a new means of therapy for ventricular arrhythmias in patients with acute myocardial infarction

In view of the current interest in the role of vagal tone on ventricular arrhythmias and the use of atropine in patients with acute myocardial infarction we have attempted to investigate the effects of vagal stimulation and atropine on ventricular vulnerability to fibrillation in normal and ischemic ventricles at a constant heart rate The possibility that the vagus nerve may exert its effect on ventricular vulnerability by an interaction with the sympathetic nerves was also tested

Methods

Experiments were performed on mongrel dogs anesthetized by a subcutaneous injection of morphine sulfate (1 5 mg per kilogram) followed in 30 minutes by an intravenous injection of α chloralose (80 to 90 mg per kilogram) This combination of anesthetics was used to preserve vagal tone of experimental dogs Under artificial respiration, the chest was opened at the midline, and the heart was cradled in the opened pericardium The sinoatrial node was crushed to permit pacing of the heart at a constant rate by applying electrical stimuli to the ventricle For reversible occlusion of the anterior descending branch of the left coronary artery the artery was dissected free for a few millimeters near its origin and a snare was applied around the vessel A femoral vein was cannulated for the administration of atropine or propranolol and a femoral artery to monitor the arterial pressure

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For vagal stimulation cervical vagi were dissected free bilaterally and decentralized by crushing Both vagi were then stimulated below a crushed area by applying square pulses of 2 msec duration at a frequency of 10 to 20 per second The voltage was gradually increased until idio ventricular escape beats appeared following a progressive slowing of the nodal pacemaker at 5 to 8 volts Atropine was administered intra venously in a dose of 0 5 mg per kilogram and propranolol was also given intravenously in a dose of 0 2 mg per kilogram Ten to 15 minutes were allowed for these agents to take effect before the test was made

The bipolar stimulating and recording elec trodes were small steel hooks with an interelec trode distance of 3 to 4 mm The stimulating electrodes were attached to the anterior septal margin of the right ventricle about 10 mm from the edge of the area of expected ischemia The recording electrodes were attached to a site close to the stimulating electrodes in the right ventri cle The local electrogram Lead II electrocardio gram and the artifact of stimuli delivered to the stimulating electrodes were all monitored on an Electronics for Medicine recorder The stimuli were also displaced on an oscilloscope and cali brated by use of a Tektronix current probe amplifier

The patterns of pacing and test stimuli delivered to the ventricle were programmed by using a variable interval generator and a series of Tektronix waveform and pulse generators The output of the pulse generator triggered a Grass stimulator which delivered 3 msec pulses to the stimulating electrodes Ventricular fibrillation threshold (VFT) was determined by delivering a train of rapid square pulses across the vulnerable period The ventricle was paced by basic stimuli at a cycle length of 400 msec and the train of rapid pulses was delivered after every twelfth basic ventricular response The rapid pulses were 3 msec in duration and occurred at 10 msec intervals (100 per second) The train was started at 80 to 100 msec after the basic response and its duration did not extend the absolute refractory period of the first premature response evoked by the train The intensity of the rapid pulses was gradually increased until fibrillation resulted The VFT was then defined as the minimum current in milliamperes which induced fibrilla tion Defibrillation was accomplished by DC

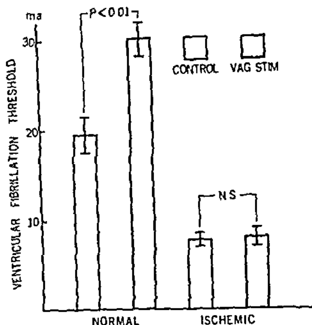


Fig 1 Effect of vagal stimulation on VFT in normal and ischemic ventricles of eight dogs. The values are expressed as means ± S E NS = not significant

countershock and 10 to 15 minutes were allowed for recovery before the subsequent test was made

Results

Vagal stimulation The effect of vagal stimula tion on VFT was studied in both normal and ischemic ventricles in eight dogs In each animal VFT's were first determined before and 3 to 5 minutes after occlusion of the anterior descending artery VFT's were determined again during vagal stimulation before and after coronary occlusion Fig 1 shows the results of these experiments In normal ventricles the mean VFT was 19 4 ± 2 1 mA in the control state before vagal stimulation and it increased significantly to 30 1 ± 2 0 mA during vagal stimulation ($P < 0.01$) In ischemic ventricles the mean VFT decreased markedly to 7 8 ± 0 8 mA before vagal stimulation ($P < 0.01$) and it remained low at 7 9 ± 1 1 mA during vagal stimulation This difference in VFT's of ischemic ventricles before and during vagal stimulation was not statistically significant ($P > 0.9$)

Atropine The effect of atropine on VFT was studied in both normal and ischemic ventricles in another seven dogs Fig 2 shows the results of these experiments In normal ventricles the mean

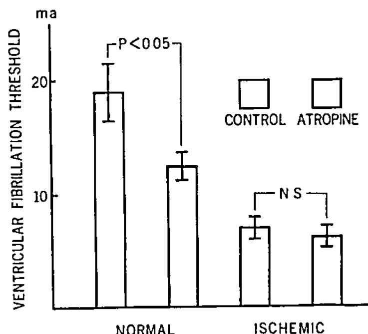


Fig 2 Effect of atropine on VFT in normal and ischemic ventricles of seven dogs The values are expressed as means ± S E NS = not significant

VFT was 18 9 ± 2 4 mA in the control state and it decreased significantly to 12 6 ± 1 3 mA after the administration of atropine ($P < 0\ 05$) In ischemic ventricles, the mean VFT was again decreased markedly to 6 9 ± 1 0 mA ($P < 0\ 01$), and it was further decreased to 6 6 ± 1 1 mA after the administration of atropine This decrease in VFT s of ischemic ventricles after atropine was very slight and not statistically significant ($P > 0\ 8$)

Propranolol pretreatment Propranolol, a β adrenergic blocking agent was used to test a possible role of the sympathetic nerves in alteration of ventricular vulnerability during vagal stimulation or after the administration of atropine VFT s were determined before and after the administration of propranolol in seven dogs with normal ventricles, and in another seven dogs with ischemic ventricles

The results obtained from normal ventricles are shown in Fig 3 The mean VFT was 14 6 ± 1 1 mA in the control state and it increased significantly to 29 0 ± 2 3 mA after the administration of propranolol ($P < 0\ 01$) Following the propranolol pretreatment, the mean VFT s were 28 3 ± 2 4 mA during vagal stimulation and 28 4 ± 3 3 mA after the atropine administration These two values were not significantly different from that observed after propranolol alone ($P > 0\ 8$) The results indicate that neither vagal stimulation nor atropine has any significant

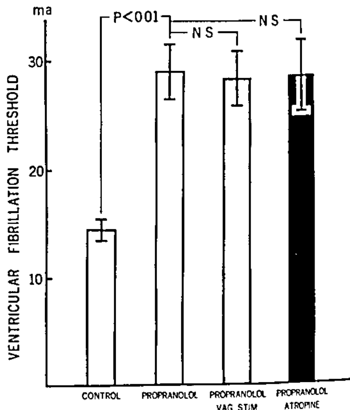


Fig 3 Effects of vagal stimulation and atropine in normal ventricles of seven dogs after the administration of propranolol The values are expressed as means ± S E NS = not significant

influence on VFT after the sympathetic activity has been blocked by propranolol

The results obtained from ischemic ventricles are shown in Fig 4 The mean VFT was low at 5 7 ± 0 7 mA in the control state before propranolol and it increased significantly to 14 1 ± 1 7 mA after the administration of propranolol ($P < 0\ 01$) Following the propranolol pretreatment, the mean VFT s were 14 1 ± 1 6 mA during vagal stimulation and 14 3 ± 1 4 mA after administration of atropine These two values were not significantly different from that obtained after propranolol alone ($P > 0\ 9$)

Discussion

Increased sympathetic tone has been known to be a contributory factor in the development of ventricular arrhythmias during acute myocardial infarction in both clinical and experimental studies [3-8] Sympathetic stimulation facilitates the development of ventricular ectopic beats by enhancing automaticity of Purkinje fibers and increasing excitability of ventricular tissues [1,9] Closely coupled ventricular extrasystoles may develop during cardiac sympathetic stimulation as a result of focal re excitation in the ventricular

myocardium It has been observed that dispersion of repolarization increases in the myocardium during stimulation of the stellate ganglia Cardiac sympathetic stimulation decreases VFT in both normal and ischemic ventricles On the other hand cardiac sympathetic denervation has been shown to decrease the incidence of ventricular arrhythmias and increase VFT in ischemic ventricles [9,10]

Recently a beneficial effect of increased vagal tone on ventricular arrhythmias and VFT has been observed in experimental animals with acute myocardial infarction [6,7] A recent study also suggested a possible adverse effect of atropine on ventricular arrhythmias during myocardial infarction The interaction of vagal and sympathetic nerves has been speculated as a possible mechanism for the beneficial effect of vagal stimulation [1] It has been shown that acetylcholine antagonizes catecholamines in myocardial cells by inhibiting catecholamine-induced increase in cyclic AMP [1] Another study has indeed demonstrated that vagal stimulation decreases the release of catecholamines from sympathetic nerve endings in the heart [3] Another possible mechanism of the beneficial effect might be that acetylcholine increases the maximum membrane potential and decreases phase 4 depolarization of Purkinje fibers Such changes are considered to improve impulse conduction and lead to electrical stability in the ventricle

The present experiments confirmed an earlier experimental observation that vagal stimulation increases VFT in normal ventricles The present study also showed that atropine decreases VFT in normal ventricles Vagal stimulation or atropine however failed to alter VFT after the sympathetic influence had been removed by propranolol The results indeed suggest that vagal stimulation may increase VFT by inhibiting the sympathetic activity It should be noted that propranolol per se increased VFT which may have resulted from the removal of underlying sympathetic tone or a direct effect of the drug on ventricular tissues or both In the present study VFT was markedly decreased in ischemic ventricles as observed in earlier studies [3,1] Vagal stimulation or atropine however failed to alter VFT significantly in ischemic ventricles In an earlier study vagal stimulation increased VFT in ischemic ventricles but the ventricular rate was not kept constant in this study [6] Since the present

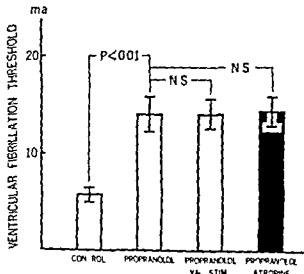


Fig 4 Effects of vagal stimulation and atropine in ischemic ventricles of seven dogs after the administration of propranolol. The values are expressed as means ± S E NS = not significant

study was conducted at a constant ventricular rate the difference between these two studies may have been due to rate related phenomena At any rate the beneficial effect of vagal stimulation on VFT could not be demonstrated in ischemic ventricles when the ventricular rate was kept constant in the present study In a recent clinical study edrophenium also failed to decrease the incidence of ventricular arrhythmias in patients during acute myocardial infarction [17]

The lack of any beneficial effect of vagal stimulation on VFT in ischemic ventricles may have been due to the overwhelming deleterious effects of myocardial ischemia Myocardial ischemia produces marked depression in excitability and conductivity in the affected area of myocardium The premature responses may therefore propagate very slowly through the ischemic area and emerge to the normal area giving rise to closely coupled re entrant beats The delayed impulse propagation through the ischemic area may allow a sufficient time for the normal area to recover and be re excited by the emerging impulse Such re entrant activity may be sustained and result in ventricular tachycardia and fibrillation [3] Whatever the mechanism of the beneficial effect of vagal stimulation might be in normal ventricles this potentially beneficial effect failed to counteract the deleterious effects of myocardial ischemia The administration of atropine also failed to influence VFT in ischemic

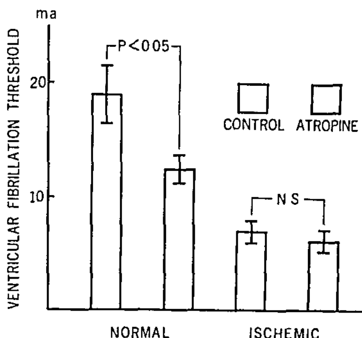


Fig 2 Effect of atropine on VFT in normal and ischemic ventricles of seven dogs The values are expressed as means ± S E NS = not significant

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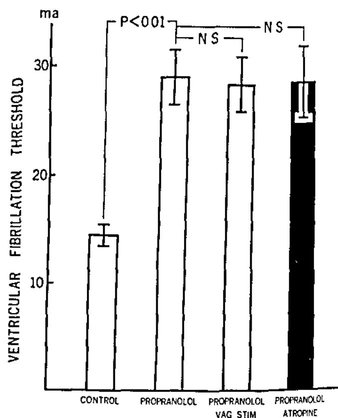


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Discussion

Increased sympathetic tone has been known to be a contributory factor in the development of ventricular arrhythmias during acute myocardial infarction in both clinical and experimental studies[2, 3, 8] Sympathetic stimulation facilitates the development of ventricular ectopic beats by enhancing automaticity of Purkinje fibers and increasing excitability of ventricular tissues[1, 9] Closely coupled ventricular extrasystoles may develop during cardiac sympathetic stimulation as a result of focal re excitation in the ventricular

threshold during experimental coronary occlusion Am J Cardiol 36 45 19 5
11 Corr P B and Gillis R A Role of the vagus nerves in the cardiovascular changes induced by coronary occlusion Circulation 49 86 1974
12 Murad F Chi, Y M Rall, T W and Sutherland E W Adenylcyclase III The effect of catecholamine and choline esters on the formation of adenosine 3' 5 phosphate by preparations from cardiac muscle and liver J Biol Chem 237 1233 1962
13 Loffelholz K and Muscholl E Inhibition by parasympathetic nerve stimulation of the release of the adrenergic transmitters, Naunyn Schmiedebergs Arch. Pharmakol. 267 181 19 0
14 Tse W W., Yoon M S and Han J Effect of acetyl choline on automaticity of Purkinje fibers, Fed Proc 34 375 19 5
15 Han J Ventricular vulnerability during acute coronary occlusion Am J Cardiol. 24 85 1969
16 Yoon M S Han J., Goel B C., and Creamer P Effect of procainamide on fibrillation threshold of normal and ischemic ventricles Am J Cardiol. 33 238 1974
17 Olson H G., Miller R R DaSilva O Amsterdam E A and Mason D T Vagal stimulation in patients with acute myocardial infarction antiarrhythmic and hemodynamic effects of edrophonium Circulation 50 III 33 1974
18 Spear J F., Moore F N and Gerstenblith G Effect of lidocaine on the ventricular fibrillation threshold in the dog during acute ischemia and premature ventricular contractions, Circulation 46 65 1972
19 Han J DeTraglia J., Millet, D and Moe G K Incidence of ectopic beats as a function of basic rate in the ventricle Am Heart J 72 632 1966
20 Chadda K D., Bunka V S and Helfant R H Rate dependent ventricular ectopia following acute coronary occlusion, Circulation 49 654 1974

ventricles However propranolol was effective in increasing VFT in ischemic ventricles as were other antiarrhythmic agents such as procainamide and lidocaine[16-18]

The beneficial effect of vagal stimulation on ventricular arrhythmias associated with myocardial infarction and the role of atropine in the treatment of these arrhythmias is still uncertain Further investigations are needed to determine whether atropine is indeed arrhythmogenic and a cholinergic agent may be used to suppress ventricular arrhythmias during myocardial infarction Recent studies have shown that both slow and rapid ventricular rates increase the incidence of ventricular arrhythmias during myocardial ischemia[1,19,20] The increased incidence of ventricular ectopic beats at slower heart rates has been attributed to an increase in the temporal dispersion of recovery of excitability and the increased likelihood of development of reentrant activity[1,19] Rapid heart rates are certain to produce the deleterious effects in ischemic ventricles since these rapidly repetitive impulses are bound to cause conduction delay in ischemic areas and ventricular ectopic beats resulting from re entry[1,15] Atropine may produce an undue increase in the heart rate and the deleterious electrophysiologic effects during myocardial infarction For this reason, the use of atropine for the treatment of bradycardia during myocardial infarction has been recently questioned However atropine may still be used in situations in which bradycardia is associated with hypotension and recurrent arrhythmias and the drug may result in a net beneficial effect

Summary

The effects of electrical stimulation of the vagus nerves and the administration of atropine on ventricular fibrillation threshold (VFT) were studied in open chest hearts of 15 dogs anesthetized by α chloralose These studies were made in both normal and ischemic ventricles i e before and during acute coronary occlusion The ventricles were paced at a constant rate to eliminate rate dependent changes and the minimal current required to induce ventricular fibrillation (or VFT) was determined by delivering a train of rapid rectangular pulses (100 per second) to the venticle across the vulnerable period In normal ventricles, VFT s were significantly increased by vagal stimulation ($P < 0.01$) and decreased by atropine ($P < 0.05$) Coronary occlusion markedly decreased VFT s ($P < 0.01$), and vagal stimulation or atropine failed to alter VFT s significantly in these ischemic ventricles ($P > 0.8$) In additional 14 dogs the effects of vagal stimulation and atropine were studied after the administration of propranolol Propranolol alone increased VFT s significantly in both normal and ischemic ventricles ($P < 0.01$) Following the pretreatment with propranolol, vagal stimulation and atropine failed to change VFT s significantly in both normal and ischemic ventricles ($P > 0.8$) These results indicate that the vagus nerves exert their effect on VFT by modifying the sympathetic nerve activity in normal ventricles but such an effect is not significant enough to alter VFT in ischemic ventricles

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REFERENCES

1 Han J Mechanisms of ventricular arrhythmias associated with myocardial infarction Am J Cardiol **24** 800 1969
2 Malling H M and Moran N C Ventricular arrhythmias induced by sympathomimetic amines in unanesthetized dogs following coronary artery occlusion Circ Res **5** 409 1957
3 Harris A S Otero H and Bocage A J The induction of arrhythmias by sympathetic activity before and after occlusion of a coronary artery in the canine heart J Electrocardiol **4** 34 1971
4 Cox W V Lewiston M E and Robeston H F The effect of stellate ganglionectomy on the cardiac function of intact dogs and its effect on the extent of myocardial infarction and on cardiac function following coronary artery occlusion AM HEART J **12** 285 1936
5 Harris A S Estandia A and Tillotson R F Ventricular ectopic rhythms and ventricular fibrillation following cardiac sympathectomy and coronary occlusion Am J Physiol **165** 505 1951
6 Kent K M Smith E R Redwood D R and Epstein S E Electrical stability of acute ischemic myocardium Influence of heart rate and vagal stimulation Circulation **47** 291 1973
7 Goldstein R E Karsh R B Smith E R Orlando M Norman D Farnham G Redwood D R and Epstein S E Influence of atropine and vagally mediated bradycardia on the occurrence of ventricular arrhythmias following acute coronary occlusion in closed chest dogs Circulation **47** 1180 1973
8 Valori C Thomas M and Shillingford J P Free noradrenaline and adrenaline excretion in relation to clinical syndromes following myocardial infarction Am J Cardiol **20** 605 1967
9 Han J Garcia de Jalon P and Moe G K Adrenergic effects on ventricular vulnerability Circ Res **14** 516 1964
10 Kliks B R Burgess M J and Abildskov J A Influence of sympathetic tone on ventricular fibrillation

Table I Hemodynamic findings in reperfused coronary vasculature before and during the intracoronary infusion of papaverine and adenosine

	Papaverine (n = 6)		Adenosine (n = 6)	
	Before	During	Before	During
HR (beats/min)	187 ± 21	183 ± 12	1[illegible]2 ± 10	171 ± 10
LVEDP (mm Hg)	9.5 ± 1.4	9.4 ± 1.5	6.7 ± 0.8	7.8 ± 1.1
AoP (mm Hg)	10[illegible] ± 9.9	103 ± 10.5	10[illegible] ± 5.8	96 ± 3.3
LAD flow (ml/min)	2[illegible].2 ± 2.4	54.9 ± 7.1†	12.7 ± 2.5	48.9 ± 9.1†
LC flow (mL/min)	32.0 ± 2.5	30.6 ± 2.2	31.6 ± 5.5	33.9 ± 6.0

Values are mean ± S.E. HR = heart rate; LVEDP = left ventricular end-diastolic pressure; AoP = aortic pressure; LAD flow = left anterior descending coronary artery blood flow; and LC flow = left circumflex coronary artery blood flow as measured by the electromagnetic flowmeter.
†P < 0.01.

these studies the vasodilator drugs were administered via a cannula in the femoral vein during coronary reperfusion. Animals in Group III (n = 5) received a 20 mg bolus of papaverine followed by an infusion of papaverine at a rate of 1 mg per kilogram of body weight per hour that was begun upon re-establishing blood flow in the LAD coronary artery.

Determination of myocardial blood flow. Measurements of myocardial blood flow in the reperfused animals of Groups I and II were made at 5 minutes and 4 hours of reperfusion and again at 4 hours of reperfusion after maximal coronary dilation with the local intra-arterial infusion of the vasodilator drug. Blood flow measurements in the nonreperfused animals (control group) were made before and following the local intra-arterial administration of the vasodilator drug. In Group III the myocardial blood flow was measured at 5 minutes, 2 and 4 hours of LAD reperfusion and papaverine administration.

Myocardial blood flow was measured by tissue trapping of 7 to 10 μ diameter radioactive microspheres (3M Co.) injected into the left atrium. By using microspheres labeled with three different isotopes (Ce, Sr, Sc) it was possible to determine myocardial blood flow under three different conditions in each animal. Following administration of the last isotope, the heart was excised and frozen for sampling. Myocardial tissue samples were taken from the left ventricular free wall in the reperfused region, from the zone bordering the reperfused region, and from the region of normal myocardium supplied by the LC coronary artery. The tissue samples were divided visually into thirds for transmural measurement of myocardial blood flow. The samples were weighed and their radioactivity

Table II Regional myocardial blood flow (milliliters per minute per gram) during the intracoronary infusion of papaverine (n = 7) and adenosine (n = 10) in normal coronary vasculature

	Control	Papaverine	Control	Adenosine
Epicardium	1.04 ± 0.20	4.77 ± 0.75	1.03 ± 0.12	4.25 ± 0.58
Endocardium	0.96 ± 0.16	4.91 ± 0.87	1.03 ± 0.12	4.11 ± 0.55

*Values are mean ± S.E.

measured by scintillation counting in a three-channel gamma counter (Nuclear Chicago 4233). Standard techniques for isotope separation were carried out with the aid of a minicomputer (DEC PDP/8E). Regional myocardial blood flow in milliliters per minute per gram was calculated by relating the radioactivity per gram of myocardial tissue to that of a reference sample of arterial blood collected at a constant rate during each administration of microspheres.[2,3]

Cardiac arrhythmias, mainly ventricular in origin, were frequently observed following the occlusion of the LAD and during the re-establishment of blood flow. To minimize the frequency of these arrhythmias or to prevent their occurrence, Lidocaine was infused at a rate of 1 mg per minute throughout the experiment. This dose of lidocaine produced no significant systemic effects.[4]

Results

Intra-arterial papaverine. The effects of an intra-arterial infusion of papaverine hydrochloride (average = 9.8 mg per minute) administered into the reperfused LAD vascular bed (Group I) are shown in Table I. The flows in both the LAD and LC were measured by flowmeters. The LAD

Coronary reperfusion Effects of vasodilators (papaverine and adenosine)

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Coronary vascular resistance has been shown to increase during coronary reperfusion following acute occlusion of a coronary artery In these previous studies we observed a progressive reduction in myocardial blood flow during reperfusion and the development of a transmural gradient in blood flow favoring the subepicardial layer of the reperfused tissue It is postulated that these hemodynamic changes are the result of swollen endothelial and perivascular cells, and red cell packing of terminal arterioles as the consequence of the ischemic process[3, 4] The present study was performed to determine the responsiveness of the reperfused vasculature to certain vasodilator agents namely papaverine and adenosine, and to examine any changes these agents might cause in the transmural gradient of myocardial blood flow in the reperfused myocardium

Materials and methods

Experiments were conducted in adult mongrel dogs anesthetized with sodium pentobarbital (30 mg per kilogram, intravenously) and ventilated with room air by Harvard respirator After exposure of the heart through a thoracotomy in the left fourth intercostal space the left circumflex (LC) and left anterior descending (LAD) coronary arteries were isolated 1 to 2 cm from their origins Electromagnetic flow transducers of appropriate size were placed on the LC and LAD and snare ligatures were placed around each artery 1 cm beyond the flow transducer Temporary tightening of these ligatures was used to verify zero coronary flow In the reperfusion studies the snare ligature was secured on the LAD for a 2 hour period, causing a large portion of the left ventricular wall to become ischemic Flow to this region was re established by releasing the snare ligature

Mean aortic pressure left ventricular end diastolic pressure LC and LAD blood flows and the limb Lead II electrocardiogram (ECG) were measured continuously Systemic arterial blood gases and pH were monitored and kept within normal physiological limits

Intra arterial vasodilator administration Maximally dilating doses of the vasodilator drugs were infused directly into the LAD following 4 hours of coronary reperfusion The local infusion was accomplished by means of a Harvard infusion pump attached to a polyethylene cannula tipped with a 25 gauge needle which was inserted directly into the artery distal to the flow transducer Animals in Group I (n = 6) received papaverine hydrochloride and those in Group II (n = 6) received adenosine The infusion rates of papaverine and adenosine were adjusted until no further increase in flow occurred as indicated by the electromagnetic flowmeter (Micron RC1000) For comparison in a control group with normal coronary circulation the effects of intra arterial infusions of both papaverine (n = 7) and adenosine (n = 10) were investigated

Intravenous vasodilator administration In

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Table III Regional myocardial blood flow (milliliters per minute per gram) during coronary reperfusion and intravenous papaverine infusion (n = 5)*

Transmural section	Normal region			Border region			Reperfused region		
	5 min.	2 hr	4 hr	5 min.	2 hr	4 hr	5 min.	2 hr	4 hr
EPI	1 89 ±0 40	1 12 ±0 14	1 23 ±0 16	2.14 ±0 50	1 18 ±0 17	1 11 ±0 14	1 99 ±0 32	0 85 ±0 11	0 65 ±0 12
MID	2.30 ±0.62	1 10 ±0 14	1 20 ±0 17	2.08 ±0 67	1 00 ±0 08	0 91 ±0 11	0 62 ±0 16	0 28 ±0 07	0 16 ±0 05
ENDO	2 15 ±0 55	1 09 ±0 13	1 18 ±0 16	2.17 ±0 65	1 16 ±0.15	1 14 ±0 18	0 77 ±0.17	0 31 ±0 08	0 15 ±0 03
Endo/Epi	1 08 ±0 10	0 98 ±0 09	0 96 ±0 07	0 97 ±0.15	1 02 ±0.12	1.03 ±0 08	0.40 ±0 08	0 41 ±0 13	0.27 ±0 08

*Values are mean ± SE

distributed transmurally (Epi = 1 40 ± 0 27 Endo = 1 41 ± 0 16 ml per minute per gram) The remaining two panels show blood flows after 4 hours of reperfusion and during the infusion of adenosine Adenosine like papaverine significantly increased blood flow to all myocardial layers in the reperfused region (Epi = 2 22 ± 0 39 Endo = 1 25 ± 0 47 ml per minute per gram) above that seen after 4 hours of LAD reperfusion alone (Epi = 0 54 ± 0 09 Endo = 0 33 ± 0 07 ml per minute per gram) The transmural gradient of flow favoring the epicardium observed following 4 hours of reperfusion was maintained during the adenosine infusion

In 10 animals with normal coronary circulation the effect of an intra arterial infusion of adenosine on the transmural distribution of flow was determined (Table II) The infusion of a maximally vasodilating dose of adenosine into the LAD coronary artery produced no significant change in heart rate left ventricular end-diastolic or systemic arterial pressure but increased myocardial blood flow 306 per cent Furthermore the measurement of myocardial blood flows in these normal hearts indicated uniform distribution transmurally before and during the infusion of adenosine

Effects of intravenous papaverine The animals in this study (Group III) received an intravenous infusion of papaverine during the 4 hour period of coronary reperfusion starting with an intravenous bolus of 20 mg of papaverine approximately 5 minutes after the onset of reperfusion The average hemodynamic parameters were not greatly affected by the papaverine infusion Aortic pressure did not change significantly except for a slight decrease upon completion of the final hour of reperfusion Left atrial pressure was transiently elevated during LAD occlusion however it was never greater than 8 mm Hg The average heart rate showed a tendency to increase during reperfusion but due to variability the changes were not statistically significant

The transmural distribution of myocardial blood flow during reperfusion with the infusion of papaverine is presented in Table III After 5 minutes of reperfusion papaverine increased blood flows to all myocardial layers This increase in flow is most likely due to the administration of the 20 mg bolus of papaverine On the second and fourth hours of reperfusion papaverine converted the expected low flow[2] in the border region to the control level and the tendency for a nonuniform distribution to a uniform one but failed to alter either the flows or their nonuniform distribution in the reperfused region as reflected by the ratio of endocardial to epicardial flows

In the reperfused region blood flows to the mid and endocardial layers were compromised more than flow to the epicardial layer and were significantly less than flows in the corresponding layers in the normal and border regions

Discussion

In previous studies re establishing blood flow to an ischemic myocardial region was accompanied by a marked increase in coronary vascular resistance which was associated with a progressive decline in the myocardial blood flow to the reperfusion region[2] Similar changes in coronary vascular resistance have been reported by others[3,4] for varying periods of coronary occlusion and reperfusion In contrast to the normal region where flow is uniformly distributed the

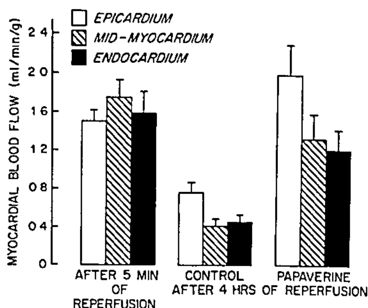


Fig 1 Transmural distribution of myocardial blood flow during coronary reperfusion at 5 minutes (left panel) at 4 hours (central panel) and after administration of papaverine into the LAD (right panel) n = 6 = P < 0 02 * = P < 0 05 statistical difference between similar myocardial layers at 4 hours of reperfusion before and after papaverine

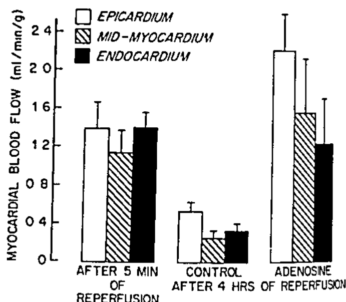


Fig 2 Transmural distribution of myocardial blood flow during coronary reperfusion at 5 minute (left panel) at 4 hours (center panel) and after administration of adenosine into the LAD (right panel) n = 6 ** = P < 0 01 = P < 0 05 statistical difference between similar myocardial layers at 4 hours of reperfusion before and after adenosine

flow rose from 22 2 to 54 9 ml per minute, an increase of 147 per cent (P < 0 01) while the blood flow in the LC coronary artery remained essentially unchanged The intra LAD infusion of papaverine exerted only a local effect in the reperfused vasculature and produced no change in other hemodynamic parameters

The effects of the intra arterial infusion of papaverine on the transmural distribution of myocardial blood flow in reperfused myocardium are shown in Fig 1 The left panel shows the myocardial blood flow following 5 minutes of reperfusion The blood flows observed 5 minutes after release of the LAD occlusion (Epi = 1 51 ± 0 11 Endo = 1 59 ± 0 23 ml per minute per gram) are slightly greater than those values usually seen in normal myocardium[2] At this time myocardial blood flow was uniformly distributed transmurally The remaining two panels show blood flows after 4 hours of reperfusion and shortly thereafter during the infusion of papaverine In agreement with flowmeter data papaverine significantly increased blood flow to all myocardial layers in the reperfused region (Epi = 2 00 ± 0 30 Endo = 1 21 ± 0 22 ml per minute per gram) above that seen after reperfusion alone (Epi = 0 76 ± 0 11, Endo = 0 46 ± 0 07 ml per minute per gram) The myocardial blood flow showed a transmural gradient favoring the epicardium (Fig 1) at 4 hours before and during papaverine

In the control group (n = 7), the effects of an intra arterial infusion of papaverine on the myocardial blood flow in the normal nonreperfused coronary vasculature are shown in Table II The infusion of a maximally vasodilating dose of papaverine into a coronary artery increased the coronary blood flow 385 per cent but produced no significant change in heart rate left ventricular end diastolic or systemic arterial pressures Thus the reperfused vasculature showed less capacity to vasodilate to papaverine than did the normal vasculature In these normal hearts uniform flow distributions transmurally were found before and during the infusion of papaverine as shown in Table II

Intra arterial adenosine Adenosine (average = 1 1 mg per minute) infused into the reperfused LAD vascular bed increased coronary blood flow while coronary blood flow in the LC artery was unchanged (Table I) The effects of the intra arterial infusion of adenosine on the transmural distribution of myocardial blood flow are shown in Fig 2 The left panel shows the myocardial blood flow following 5 minutes of reperfusion At this time myocardial blood flow was uniformly

Table III Regional myocardial blood flow (milliliters per minute per gram) during coronary reperfusion and intravenous papaverine infusion (n = 5)

Transmural section	*Normal region*			*Border region*			*Reperfused region*		
	5 min.	*2 hr*	*4 hr*	*5 min.*	*2 hr*	*4 hr*	*5 min.*	*2 hr*	*4 hr*
EPI	1.89 ±0.40	1.12 ±0.14	1.23 ±0.16	2.14 ±0.50	1.18 ±0.17	1.11 ±0.14	1.99 ±0.32	0.85 ±0.11	0.66 ±0.12
MID	2.30 ±0.62	1.10 ±0.14	1.20 ±0.17	2.08 ±0.67	1.00 ±0.08	0.91 ±0.11	0.62 ±0.16	0.28 ±0.07	0.16 ±0.05
ENDO	2.15 ±0.55	1.09 ±0.13	1.18 ±0.16	2.17 ±0.65	1.16 ±0.15	1.14 ±0.18	0.77 ±0.17	0.31 ±0.08	0.15 ±0.03
Endo/Epi	1.08 ±0.10	0.98 ±0.09	0.96 ±0.07	0.97 ±0.15	1.02 ±0.12	1.03 ±0.08	0.40 ±0.08	0.41 ±0.13	0.27 ±0.08

Values are mean ± S.E

distributed transmurally (Epi = 1.40 ± 0.27 Endo = 1.41 ± 0.16 ml per minute per gram) The remaining two panels show blood flows after 4 hours of reperfusion and during the infusion of adenosine Adenosine like papaverine significantly increased blood flow to all myocardial layers in the reperfused region (Epi = 2.22 ± 0.39 Endo = 1.25 ± 0.47 ml per minute per gram) above that seen after 4 hours of LAD reperfusion alone (Epi = 0.54 ± 0.09 Endo = 0.33 ± 0.07 ml per minute per gram) The transmural gradient of flow favoring the epicardium observed following 4 hours of reperfusion was maintained during the adenosine infusion

In 10 animals with normal coronary circulation the effect of an intra arterial infusion of adenosine on the transmural distribution of flow was determined (Table II) The infusion of a maximally vasodilating dose of adenosine into the LAD coronary artery produced no significant change in heart rate left ventricular end diastolic or systemic arterial pressure but *increased* myocardial blood flow 306 per cent Furthermore the measurement of myocardial blood flows in these normal hearts indicated uniform distribution transmurally before and during the infusion of adenosine

Effects of intravenous papaverine The animals in this study (Group III) received an intravenous infusion of papaverine during the 4 hour period of coronary reperfusion starting with an intravenous bolus of 20 mg of papaverine approximately 5 minutes after the onset of reperfusion The average hemodynamic parameters were not greatly affected by the papaverine infusion Aortic pressure did not change significantly except for a slight decrease upon completion of the final hour of reperfusion Left atrial pressure was transiently elevated during LAD occlusion however it was never greater than 8 mm Hg The average heart rate showed a tendency to increase during reperfusion but due to variability the changes were not statistically significant

The transmural distribution of myocardial blood flow during reperfusion with the infusion of papaverine is presented in Table III After 5 minutes of reperfusion papaverine increased blood flows to all myocardial layers This increase in flow is most likely due to the administration of the 20 mg bolus of papaverine On the second and fourth hours of reperfusion papaverine converted the expected low flow[2] in the border region to the control level and the tendency for a nonuniform distribution to a uniform one but failed to alter either the flows or their nonuniform distribution in the reperfused region as reflected by the ratio of endocardial to epicardial flows

In the reperfused region blood flows to the mid and endocardial layers were compromised more than flow to the epicardial layer and were significantly less than flows in the corresponding layers in the normal and border regions

Discussion

In previous studies re-establishing blood flow to an ischemic myocardial region was accompanied by a marked increase in coronary vascular resistance which was associated with a progressive decline in the myocardial blood flow to the reperfusion region[2] Similar changes in coronary vascular resistance have been reported by others[7,8] for varying periods of coronary occlusion and reperfusion In contrast to the normal region where flow is uniformly distributed the

flow to the reperfused region is nonuniformly distributed, with the endocardial layer most severely compromised[2] These changes in both flow and resistance have been explained on the basis of structural changes in the reperfused vasculature consisting of swelling of endothelial and perivascular cells as well as myocardial cell swelling, interstitial edema[12] and microthrombi[11]

In an attempt to determine whether these changes following coronary reperfusion are solely responsible for the observed increase in resistance or the result of some active vasoconstrictive element, the effects of known coronary vasodilators were evaluated by administering these agents locally into the left anterior descending coronary artery and intravenously through the femoral vein Both papaverine and adenosine increased total myocardial blood flow without disturbing the observed nonuniformity of this flow across the reperfused myocardium Barner and associates[9] examined the effects of papaverine on coronary blood flow in man following saphenous vein coronary bypass Twenty to 30 minutes after discontinuation of extracorporeal bypass the intra arterial administration of papaverine into the graft produced a 215 per cent increase in coronary blood flow Despite the dissimilarities between the two studies, their finding in man is confirmed by our present observation of an increase in flow This increase is noted to occur in all layers of the reperfused myocardium This increase in myocardial flow occurred in the absence of any significant hemodynamic changes and could only be ascribed to its vasodilating effect and not secondary to its inotropic action on the myocardium

The site of the observed increase in myocardial blood flow following papaverine administration is either through the existing nutritive vessels or through non nutritive arteriovenous anastomoses or through both channels The observation of Kane and associates[13] of a significant reduction in the arteriovenous oxygen difference across the reperfused region which persisted throughout the 2 hour period of reperfusion may represent the opening of A V shunts In the present study, the myocardial blood flow is measured by the tissue trapping of radioactive microspheres with a diameter of 7 to 10 μ Increased trapping of these microspheres during vasodilator administration would reflect an increase in nutritive flow rather than an increase in flow in non nutritive A V shunts since the small microspheres should pass through these shunts Furthermore, by the second hour of reperfusion, the myocardial blood flow was markedly reduced rather than increased as would be expected if these shunts were operational However, the remote possibility that A V shunts appear in reperfused tissue could not be totally discounted

In the normal coronary bed, the intracoronary infusion of a maximally vasodilating dose of papaverine that produced no change in heart rate, left atrial pressure, or systemic arterial pressure increased flow in the nonreperfused region by + 348 per cent This is in contrast to the moderate increase in flow in the reperfused region suggesting that the reperfused vasculature had less capacity to vasodilate to papaverine than did the nonreperfused normal vasculature This observation supports our previous suggestion[1, 2] of the development of an increased passive or structural component of resistance in the reperfused coronary vasculature during the coronary reperfusion It is conceivable however, that the anatomical vascular changes have resulted both in a reduced capacity of the reperfused vasculature to allow an increase in blood flow through its lumen and in a diminished ability of the vasculature smooth muscle to dilate It is believable that these two factors are active simultaneously in the reperfused region and that through its effects on the smooth muscle papaverine increased the myocardial blood flow to the reperfused region

In the normal myocardium papaverine distributed uniformly the increased flow to all the layers of the myocardium In the reperfused myocardium, while increasing the flow to all layers of the myocardium, papaverine failed to alter the observed nonuniform distribution of flow seen in the reperfused region This observation would suggest, perhaps that the structural changes in the coronary vasculature in the deep layers of the myocardium are more severely affected and this is consistent with the observation of Krug[10] who noted an early change in H concentration in the inner third of the myocardium In spite of the possibility that the endocardial layer is supplied with a relatively greater number of vessels,[14] it is reasonable to assume that if the inner layer of the myocardium is first to be affected by the ischemic

process more severe structural changes would be expected in this layer if the ischemic period is extended[2]

The finding of abnormal structural vascular changes in the reperfused myocardium and the persistent reduction in coronary blood flow are consistent with the reported metabolic derangement following coronary reperfusion where increased potassium loss and abnormal lactate metabolism were noted in both the reperfused ischemic and borderline regions[2] Increasing coronary blood flow by means of pharmacologic agents might prove beneficial in salvaging injured myocardium Following systemic administration of papaverine myocardial blood flow to the border region areas between the ischemic and normal myocardium improved markedly The flow to this region returned to normal and was uniformly distributed The total myocardial flow and its transmural distribution to the ischemic reperfused region were similar to those described above accompanying the intra arterial administration of papaverine It appears that papaverine infused during the period of reperfusion plays a significant role in maintaining myocardial flow to the zone bordering the reperfused region Thus this intervention may be more useful in protecting moderately ischemic tissue than in saving severely damaged myocardium

The behavior of the coronary vasculature to adenosine is essentially similar to that observed following the intra arterial papaverine infusion The intracoronary administration of adenosine also resulted in a marked increase in myocardial blood flow to the epicardial mid and endocardial layers The nonuniform distribution of blood flow favoring the epicardium that existed following 4 hours of reperfusion was again maintained during maximal dilation of the reperfused coronary vasculature with adenosine In the normal nonreperfused heart the intracoronary administration of either adenosine or papaverine resulted in a marked increase in myocardial blood flow that was uniformly distributed transmurally

Summary

Reperfusion of a coronary artery is followed by a decline of the myocardial blood flow to both the ischemic (reperfused) and border regions and the appearance of a transmural flow gradient favoring the epicardium These findings were ascribed to vascular changes in the reperfused coronary bed The behavior of the myocardial blood flow was investigated (1) after 4 hours of reperfusion following the intracoronary infusion of vasodilators (papaverine and adenosine) and (2) following the intravenous administration of papaverine during the total period of reperfusion

Intracoronary infusion of vasodilators increased flow (147 per cent) to all the layers of the reperfused myocardium but failed to alter the transmural distribution of flow The flow response to these vasodilators in the normal vascular bed consisted of a marked increase in flow (385 per cent) and a normal uniform distribution suggesting that the development of anatomical vascular changes reduced the capacity of the reperfused vasculature to increase flow and that these changes were more marked in the endocardial layer The intravenous papaverine infusion during reperfusion normalized the total flow and its distribution in the zone bordering the reperfused myocardium but not to the ischemic suggesting perhaps that papaverine may be useful in protecting potentially salvageable myocardium

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REFERENCES

1 Parker P E Bashour F A., Downey H F., and Kechejian, S J Distribution of myocardial blood flow during coronary reperfusion before and after papaverine Clin Res 22 630A 1974
2 Parker P E Bashour F A Downey H F Kechejian S J., and Williams A G Coronary hemodynamics during reperfusion following acute coronary ligation in dogs AM HEART J 90 593 1975
3 Flores J D R Di Bona D R Beck C H and Leaf A Role of cell swelling in ischemic renal damage and the protective effect of hypertonic solute J Clin Invest 51 118 1972
4 Summers W K and Jamison R L. The no reflow phenomenon in renal ischemia Lab Invest 25 635 1971
5 Makowski, E L. Meschia G Droegemueller W., and Battaglia F C Measurement of umbilical artery blood flow to the sheep placenta and fetus in utero Circ Res 23 623 1968
6 Bashour F A Downey H F Geumei, A M Kechejian S J Underwood, R H and Williams, A G Coronary vascular response to lidocaine Clin Res 21 860 1973
7 Willerson J T Watson J T Hutton I Templeton G H and Fixler D F Reduced myocardial reflow and increased coronary vascular resistance following prolonged myocardial ischemia in the dog Circ Res 36 771 1975

8 Kloner R A Ganote C E and Jennings R B The no reflow phenomenon after temporary coronary occlusion in the dog J Clin Invest 54 1496 1974
9 Barner H B Kaiser G C and Willman V L Effect of nitroglycerin and papaverine on coronary flow in man AM HEART J 88 13 1974
10 Krug A Alterations in myocardial hydrogen ion concentration after temporary coronary occlusion a sign of irreversible cell damage Am J Cardiol 36 214 1975
11 Lang T W Corday E Gold H Meerbaum S Rubins S Constantini C Hirose S Osher J and Rosen V Consequences of reperfusion after coronary occlusion Am J Cardiol 33 69 1974
12 Meerbaum S and Corday E Symposium on reperfusion during acute myocardial infarction Am J Cardiol 36 211 1975
13 Kane J Murphy M Bisett J De Soyza N Doherty J and Straub K Mitochondrial function oxygen extraction epicardial S T segment changes and tritiated Digoxin distribution after reperfusion of ischemic myocardium Am J Cardiol 36 218 1975
14 Downey, H F Bashour F A Boatwright R B Parker P E and Kechejian S J Uniformity of transmural perfusion in anesthetized dogs with maximally dilated coronary circulations Circ Res 37 111 1975

Cardiac pathology of transvenous pacemakers in dogs

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Transvenous cardiac pacemakers have been of great benefit to many patients with complete heart block Long term implantation of such devices however is accompanied by morphologic changes in the heart which may interfere with pacemaker function Patients in whom such complications have occurred have been the subject of numerous reports [1-5] Similar morphologic changes also have been observed in experimental animals with intracardiac pacemaker electrodes [6-7] This study was undertaken to examine in greater detail the cardiac pathology associated with long term implantation of transvenous cardiac pacemakers in dogs We have attempted to determine how often these changes might occur and how they affect pacemaker and cardiac function and attempts to remove unneeded or nonfunctional pacemaker catheters

Materials and methods

Unipolar or bipolar transvenous cardiac pacemaker catheters made of medical grade silicone rubber with platinum-10 per cent iridium electrodes were implanted in the right ventricular cavities of 18 mongrel dogs Sterile catheters and aseptic techniques were used Complete heart block was produced in 15 dogs by injection of 37 per cent formaldehyde into the interatrial septum in the region of the atrioventricular node This was accomplished either by transvenous injection through a catheter ensheathed needle positioned against the interatrial septum or by injection through the pericardium and right atrial wall after thoracotomy [16] Pacing rates varied from 72 to 102 beats per minute and pacemaker function was monitored by periodic electrocardiograms In three of the 18 dogs no attempt to produce heart block was made Pacemaker catheters were implanted in these three animals but no electrical stimulation was applied Implantation periods varied from 2 to 18 months (average 4 9 months) The dogs received perioperative broad spectrum antibiotics and were maintained on normal diets After the animals had been put to death the hearts were removed with catheters in place and postmortem cardiac roentgenograms were made to determine the exact position of each catheter in the right ventricular cavity Following gross examination formalin fixed tissues were processed and stained by the following methods hematoxylin and eosin Masson s trichrome Verhoeff's elastic stain and MacCallum Goodpasture stain for gram positive and gram negative organisms

Results

Heart weights varied from 140 to 300 grams (average 231 grams) Cardiac hypertrophy defined as heart weight greater than 1 per cent of body weight [19] was present in eight of 15 dogs paced and in none of the three control dogs which were not paced Gross (Figs 1 and 2) and microscopic (Figs 3 to 13) pathologic findings varied somewhat in all 18 dogs however the variability was not related to heart rate or whether or not the electrodes were stimulated The most striking

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Fig 1 Heart of dog with pacemaker catheter implanted and stimulated for 4 months Note tubular encapsulation of catheter in the posterior leaflet of the tricuspid valve (*TV*) and right ventricular cavity (*RV*) Endocardial papillary thickening (arrow) is present in the right atrium



Fig 2 In this control dog the catheter was implanted for 3 months but no electrical stimulation was applied Note endocardial papillary thickening of the tricuspid valve leaflets and right ventricle (arrows) and entrapment of the catheter tip

gross morphologic findings could be separated into four major groups (1) fibrous sheath formation around the catheters (2) endocardial papillary thickening (3) interatrial septal changes and (4) myocardial damage

Sheath formation The intracardiac catheters were encapsulated or ensheathed in one or more locations within the heart in all 18 dogs (Figs 1 and 2) This occurred in right atrium of nine tricuspid valve of seven and right ventricle of 14 of the 18 animals The walls of these firm tubular connective tissue sheaths measured up to 3 5 mm in thickness and were tightly adherent to the catheters from which they were difficult to dissect free When sheaths had formed in the tricuspid valve the catheters passed between chordae tendineae and were completely encircled by the involved valve leaflets Histologically (Figs 3 to 8), sheaths consisted of dense fibrous tissue composed of both collagen and elastic fibers with focal infiltrates of polymorphonuclear leukocytes and larger infiltrates of lymphocytes plasma cells and histiocytes Hemosiderin granules were found in macrophages and extracellularly in the connective tissue Foci of cartilagenous metaplasia, characterized by cells with spherical nuclei in lacunae embedded in a homogeneous matrix were present in all nine right atrial all seven tricuspid valvular and 12 of 14 of the right ventricular sheaths which had formed around the catheters In some animals fragments of foreign material presumably from the catheters, could be identified along the inner surfaces of sheaths (Fig 8) In some regions a single layer of endothelial cells lined the sheaths In other areas no endothelial cell layer was evident Foci of calcification were present in four of the right ventricular sheaths The fibrosis metaplasia and inflammation extended into myocardium underlying affected endocardium Although usually superficial in some areas the myocardial involvement was almost transmural (Fig 5)

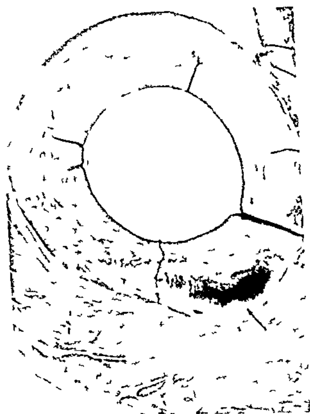


Fig 3 Low power cross sectional view of right ventricular sheath which had proliferated around an implanted catheter Note an area of cartilagenous metaplasia (arrow) shown at higher power in Fig 4 (Hematoxylin and eosin ×14)



Fig 4 Higher power of a sheath similar to that of Fig 3 showing round cells in lacunae surrounded by an interstitial matrix characteristic of cartilage Chronic inflammatory cells are present in the sheath. (Hematoxylin and eosin ×70)

Endocardial papillary thickening Areas of marked endocardial thickening were present in right atrium tricuspid valve and right ventricle whether or not sheaths were present (Figs 1 and 2) however the endocardial thickening tended to be more diffuse in regions where the catheters were not encapsulated In some areas the thickened endocardium was grossly papillary in configuration Microscopically (Figs 9 to 12) the thickened endocardium was covered by a layer of squamous to cuboidal endothelial cells In several foci, there was an increased number of the cuboidal cells which had round oval and irregular nuclei rather than thin flat nuclei usually found in normal endothelium Beneath the surface similar if not identical cells were present In addition there were other cells which were polygonal columnar and spindle shaped Many of these cells were adjacent to the endocardial surface The thickened endocardium also contained collagen and elastic fibers and infiltrates of acute and chronic inflammatory cells Foci of cartilagenous metaplasia were present in thickened endocardium and were surrounded by spindle shaped fibrocytic cells Underlying myocardium was involved by the fibrosis metaplasia and inflammation

Interatrial septal changes Marked alterations in the interatrial septum in the region of the A V node and bundle where formaldehyde was injected to produce heart block were present Grossly there was thickening consisting of firm white tissue which extended into the myocardium and often into tricuspid valve leaflets Histologically (Fig 13) these areas were composed primarily of large areas of cartilagenous metaplasia surrounded by dense collagen Focal infiltrates of lymphocytes plasma cells and histiocytes were present Hemosiderin granules were evident in macrophages and extracellularly in connective tissue

Myocardial changes Myocardium remote



Fig 5 Longitudinal section of sheath from a dog with a functioning pacemaker implanted for 18 months Note marked cellular infiltrate surrounding the sheath and extending into adjacent myocardium (see Fig 6) (Hematoxylin and eosin ×8)

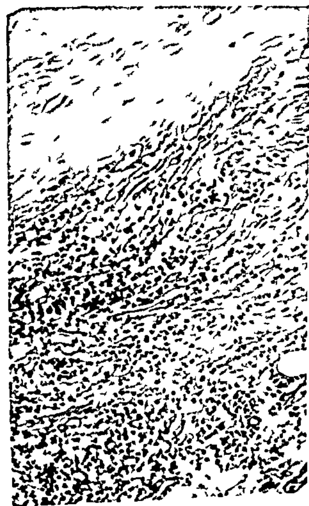


Fig 6 Lymphocytic infiltrate beneath connective tissue (Hematoxylin and eosin ×150)



Fig 7 Randomly oriented elastic fibers in endocardial sheath (Verhoeff's elastic stain ×480)

from damaged endocardium showed only focal fatty infiltration and small focal infiltrates of lymphocytes with no necrosis or fibrosis Severe myocardial damage was found in areas underlying abnormal endocardium (Fig 5)

The remainder of the cardiac valves and chambers had no endocardial or myocardial abnormalities No infectious organisms were identified

Discussion

This study shows that chronic implantation of pacemaker catheters in dog hearts consistently produces significant pathologic changes which may interfere with cardiac function pacemaker function and subsequent catheter removal Fibrous encapsulation of the catheters and endocardial thickening occur at various sites within the heart—namely right atrium tricuspid valve and right ventricle Histologically these lesions are composed of fibrous tissue inflammatory cells and areas of cartilagenous metaplasia and marked proliferation of endocardial cells

Encapsulation of the catheters occurred in all dogs studied Fibrous encapsulation or entrapment of the catheters has been described in patients dying after chronic implantation of pacemakers and in a number of experimental animals studied [6-7] Lagergren and associates [1] in a study of 142 patients with pacemakers noted such encapsulation in 12 of 15 patients autopsied in whom the electrodes were in place 1 week or longer They found no correlation between the thickness of the capsule and duration of implantation Robboy and associates[2] studied autopsy data from seven patients dying after receiving pacemakers and found fibrosis around catheters in five of six in whom the implantation period was greater than 1 5 months In four of their patients the electrodes were adherent to the chordae tendineae of the tricuspid valve Parsonnet and associates [8] in one of the few long term anatomic studies in experimental animals noted fibrous encapsulation of the catheters in eight of nine dogs studied These authors also noted rising thresholds for stimulation in these animals and suggested that such increases were related to connective tissue proliferation around the electrodes Because of fibrous encapsulation these authors and others[2 7 2 2] have implied that safe removal of chronically implanted catheters may be difficult The frequency with which this complication occurs however is unknown The



Fig 8 Remnants of catheter tightly adherent to fibrous sheath following postmortem removal of the catheter (Trichrome ×400)

findings of this study suggest that virtually all intracardiac electrodes eventually will become entrapped at some intracardiac location (right atrium tricuspid valve or right ventricle) and any vigorous attempts to remove them by manipulation [7] continued traction[21] or by intracardiac operative procedures[22] may cause damage to cardiac structures

When encapsulation occurs in the tricuspid valve leaflets it may interfere with valvular function as well as attempts to remove the catheters Similarly affected tricuspid valves have been observed in humans by Robboy and associates [2] Becker and associates [3] Furman and Escher Friedberg and D cunha [5] and Huang and Baba [6] In none of these patients reported however was there clinical evidence of tricuspid valvular dysfunction The appearance of the tricuspid valves of dogs of this study suggests that dysfunction of such valves may occur more often than reported and should be sought for in



Fig 9 Section of right atrial wall showing marked papillary thickening of the endocardium also present in right ventricle (see Figs 1 and 2) Foci of cartilage are present at the junction between endo and myocardium (arrows) (Hematoxylin and eosin ×9 5)



Fig 10 Papillary thickening of the tricuspid valve leaflet shown grossly in Fig 2 (Hematoxylin and eosin ×7)

patients with intracardiac pacemaker catheters

Endocardial papillary thickening in the dogs o this study appears to be related to mechanica trauma to areas in contact with the implante catheters This tissue showed remarkable cellula as well as connective tissue proliferation Al though many of these cells were fibrocytic, other were similar to those of the endocardial endothe lium Rodbard and associates[23] produced simila papillary cellular lesions in left atria of dogs b creating an endocardium covered interatrial mas which contacted other areas of the endocardium These authors suggested that such lesions de velop where different areas of endocardium are i sliding contact and that frictional forces ma contribute to the genesis of these growths Cel lular proliferation also occurs in areas of th vascular tree where blood flow is most turbulent and in other lesions such as the endocardia papillary elastofibroma [5] We are unaware of previous reports of papillary endocardial prolifer ation in association with intracardiac catheters Since these changes occurred in the dogs whether or not external electrical stimulation was applied it appears that mechanical trauma alone and not external electrical stimulation was responsible for these proliferations Although infective endo carditis must be considered as a possible cause for



Fig 11 Marked endothelial cell hyperplasia from an area of endocardial thickening Most of this area is covered by plump cells with irregular nuclei. A few normal appearing squamous endothelial cells remain (arrow) (Hematoxylin and eosin ×693)



Fig 12 Section through another area of thickened ventricular endocardium. Note the variable appearance of the cells, some of which are spindle shaped Acute inflammatory cells are present (Hematoxylin and eosin ×72·)

such lesions the use of sterile materials aseptic techniques and perioperative antibiotics makes infection less likely—especially since there was no histologic evidence of infectious agents

Cartilagenous metaplasia in areas of endocardial and myocardial scarring was another consistent finding in the dogs studied whether or not there was electrical stimulation Such changes occurred in areas of endocardium and myocardium traumatized by the catheters and in interatrial septum where formaldehyde was injected to produce heart block Thus both mechanical and chemical irritation produced this change Similar changes have been produced in bird aortas and other animal tissues by mechanical and chemical stimulation[26] Metaplasia the transformation of one mature cell type to another[27] is a response to chronic irritation or injury Cartilage is frequently present in normal canine cardiac structures such as the central fibrous body of the heart and aortic root[9] and in some canine neoplasms It appears that canine tissues readily undergo cartilagenous metaplasia as a nonspecific response to tissue alteration secondary to inflammatory degenerative or neoplastic processes

Severe myocardial damage with intracavitary cardiac catheters occurs predominantly in areas adjacent to altered endocardium and appears to be a direct extension of the pathologic changes in endocardium Such damage may be extensive and could cause significant myocardial dysfunction or failure Such areas could also be sites of ventricular irritability and arrhythmias Increases in myocardial pacing thresholds commonly occurs with chronic pacing In a study of 75 patients, Contini and associates[1] noted a rise in pacing threshold from a mean of 1 3 volts at implantation to 2 6 volts 3 months later They ascribed this rise to a nonspecific foreign body inflammatory reaction to the electrode Parsonnet and associates thought such increases in pacing thresh



Fig 13 Appearance of heart into which formaldehyde had been injected into conductive tissue of the interatrial septum to produce heart block This area is replaced by metaplastic cartilage (inset Hematoxylin and eosin ×150) which extends into the right atrial myocardium (*RA*) and involves the right atrial and right ventricular (*RV*) endocardium Tricuspid valvular tissue is obliterated by the process (Hematoxylin and eosin ×6 5)

olds were related to fibrous tissue proliferation between the electrode and myocardium It seems reasonable to assume that the marked connective tissue proliferation observed may decrease current density around the electrodes until pacing no longer occurs No information is available concerning differential effects of different types of tissue (such as cartilage) on pacing thresholds and current densities Progressive increases in electrical stimulation needed for pacing may be related to progressive proliferation of endocardial and myocardial connective tissues When pacemaker failure occurs it may be related to such proliferation Future quantitative studies relating pacing thresholds to implant periods connective tissue proliferation inflammatory cell infiltration, and cellular proliferations in endocardium may be helpful in predicting if and when pacemaker failure will occur Such information should be useful in decreasing morbidity and mortality associated with unexpected pacemaker failure

Summary

Transvenous right ventricular pacemaker catheters were implanted in 18 mongrel dogs for periods of 2 to 18 months (average 4 9 months) Heart block was produced in 15 of these dogs by injection of 37 per cent formaldehyde into the interatrial septum In the other three dogs which served as controls, no heart block was produced and no electrical stimulation was applied to the implanted catheters After the animals had been put to death gross and microscopic examination of the hearts revealed four categories of morphological changes (1) connective tissue sheath formation around the catheters (2) endocardial papillary thickening (3) interatrial septal changes and (4) myocardial damage Changes 1 2, and 4 occurred in one or more intracardiac locations in all 18 dogs Change 3 occurred only in the 15 dogs in which heart block was produced The most striking histologic findings were areas of cartilagenous metaplasia in endocardium and underlying myocardium and areas of marked cellular proliferation of the endocardial cells both in the endothelium and underlying stroma Chronic implantation of transvenous intracardiac pacemaker catheters in dogs consistently produces morphologic changes which may interfere with cardiac and pacemaker function and may hinder attempts to remove nonfunctional or unneeded catheter electrodes The changes observed appear to be related to the presence of foreign material *per se* and not external electrical stimulation of the heart

REFERENCES

1 Lagergren H Dahlgren S and Nordenstam H Cardiovascular tissue response to intracardiac pacemaking Acta Chir Scand **132** 696 1966
2 Robboy S J Harthorne J W Leinbach R C Sanders C A and Austen W G Autopsy findings with permanent pervenous pacemakers Circulation **39** 495 1969
3 Becker A E Becker M J Claudon D G and Edwards J E Surface thrombosis and fibrous tissue encapsulation of intravenous pacemaker catheter electrode Circulation **46** 409 1972
4 Furman S and Escher D J W Retained endocardial pacemaker electrodes J Thorac Cardiovasc Surg **55** 737 1968
5 Friedberg H D and D cunha G F Adhesions of pacing catheter to tricuspid valve adhesive endocarditis Thorax **24** 498 1969
6 Huang T and Baba N Cardiac pathology of transvenous pacemakers AM HEART J **83** 469 1972

7 Contini, C., Papi L. Pesola A. L'Abbate A. Magini, G. D'angelo T., Cinacchi, P., Maseri, A., and Donato L. Tissue reaction to intracavitary electrodes effect on duration and efficiency of unipolar pacing in patients with A V block J Cardiovasc Surg 14 ?8? 1973
8 Gotsman M S Piller L. W., Beck W Barnard C N and Schrire V Some problems of permanent artificial pacing Br Med J 1 343 1968
9 Imparato A M and Kim G E Electrode complications in patients with permanent cardiac pacemakers Ten years experience Arch Surg 105 705 1972
10 Petterson S R, Singh J B Reeves G and Kocot S L. Tricuspid valve perforation by endocardial pacing electrode Chest 63 126 1973
11 Battle W E Banas, J S Jr and Levine H J Papillary muscle rupture of the mitral valve complicating removal of a permanent transvenous electrode Chest 63 455 1973
12 Fishenfeld J and Lamy Y Laceration of the tricuspid valve by a pacemaker wire Chest 61 697 1972
13 Friedman S A Berger N Cerruti, M M and Kosmoski J Venous thrombosis and permanent cardiac pacing AM HEART J 85 531 1973
14 Haupt G J Myers R N Perrill C V and Birkhead N C Human tissue response to long term implanted cardiac pacemaker-electrode system Surg Gynecol Obstet 117 484 1963
15 Wertheimer M Hughes R K and Castle H Superior vena cava syndrome Complication of permanent transvenous endocardial cardiac pacing J A M A 224 11?? 1973
16 Parsonnet V Zucker I R Kannerstein M L., Gilbert L and Alvares J F The fate of permanent intracardiac electrodes J Surg Res. 6 285 1966
17 Cummings J R Gelok R Grace J L River P and Sulkind A J Long term evaluation in large dogs and sheep of a series of new fixed rate and ventricular synchronous pacemakers, J Thorac Cardiovasc Surg 66 645 1973
18 Starzl T E and Gaertner R A Chronic heart block in dogs. A method for producing experimental heart failure Circulation 12 259 1955
19 Miller M F Christensen G C., and Evans H E Anatomy of the dog Philadelphia 1968 W B Saunders Company
20 Kosowsky B D and Barr I Complications and malfunctions of electrical cardiac pacemakers, Prog Cardiovasc. Dis 14 501 1972
21 Bilgutay A M Jensen N K Schmidt W R Garamella J J., and Lynch, M F Incarceration of transvenous pacemaker electrode Removal by traction AM HEART J 77 377 1969
22 Yarnoz, M D Attai, L. A., and Furman S Infection of pacemaker electrode and removal with cardiopulmonary bypass, J Thorac Cardiovasc Surg 68 43 1974
23 Rodbard S Kinoshita Y and Montes, M Induction of papillary growths in the heart Science 143 1341 1964
24 Flaherty J T Pierce J E., Ferrans, V J Patel D J., Tucker K W and Fry D L. Endothelial nuclear patterns in the canine arterial tree with particular reference to hemodynamic events Circ Res 30 23 1972
25 Fishbein M C., Ferrans V J and Roberts W C Endocardial papillary elastofibroma. Histology histochemistry and electron microscopy Arch. Pathol. 99 335 1975
26 McCandless E L. Lehoczky J M and Rodbard S Aortic cartilage produced by intramural carrageenan Arch. Pathol 75 507 1963
27 Anderson W A D Pathology St Louis 1971 The C V Mosby Company Vol I
28 Smith H A and Jones T C Veterinary pathology Philadelphia 1966 Lea & Febiger Publishers

Attenuation of cardiac sympathetic drive in experimental myocardial ischemia in dogs

Mario Feola*
Emanuel R Arbel
Gerald Glick
With the technical assistance of Anthony Ellis
Chicago Ill

It has been proposed that bradycardia and hypo tension, which are frequently found in the early phase of acute myocardial infarction [1,2] are due to a reflex of the Bezold Jarisch type [3,8] *Activa* tion of mechanoreceptors present in the left ventricle[9,10] by stretching and bulging of *the* ischemic area[11] has been found reflected in an increased neural traffic in *afferent vagal* fibers [1,14] Central stimulation of these fibers has produced bradycardia, hypotension, and periph eral vasodilation[15], vagotomy, before and *after* coronary occlusion, has prevented or reduced the occurrence of these changes [3,6,8,16] These *find* ings however, have been disputed and the func tional significance of this reflex has been ques tioned by many [17,1]

Most studies have focused mainly on peripheral vasomotor responses and only two contradictory observations have been reported in which efferent sympathetic nerve activity to the heart was measured directly Costantin[1] described in cats a transient decrease of sympathetic discharge recorded from the left inferior cardiac nerve which lasted about 60 seconds In contrast, Malliani and associates reported an increase of activity in the preganglionic sympathetic cardiac fibers contained in the T_3 ramus communicans, also in cats

It was, therefore, considered of interest to analyze (1) whether the efferent cardiac sympa thetic response to acute coronary occlusion wa *one of* increased or decreased activity, (2) whethe this response was a transient change or sustained phenomenon and (3) whether it migh represent, through a reduction of contractile forc and cardiac output a contributing factor in th pathophysiology of cardiogenic shock

Methods

Healthy adult dogs weighing between 15 and *25 kilograms* were anesthetized with intravenous alpha chloralose (100 mg per kilogram of body weight) *and urethan* (500 mg per kilogram) placed on an electric pad to keep body tempera ture *at 37 to 38°C* intubated with a cuffed endotracheal tube and ventilated with room air and 40 per cent oxygen by means of a Harvard respirator To obtain complete *muscle relaxation* succinylcholine (10 mg per kilogram per hour) *was infused* when necessary The endotracheal tube was connected to a Statham pressure trans ducer which allowed monitoring of respiratory movements Subcutaneous electrodes were placed in the limbs to *monitor* the electrocardiogram (ECG) Teflon catheters 10 inches in length were *inserted* through the femoral artery into the central aorta and through the femoral *vein into* the inferior vena cava, and connected to P23db

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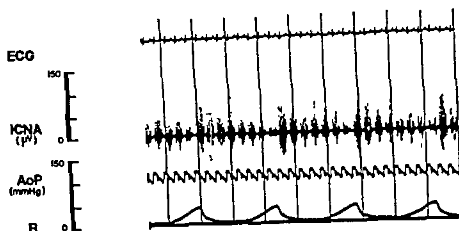


Fig 1 Original tracing showing the cardiac rhythmicity of a few fiber preparations obtained from the inferior cardiac nerve Note that nerve activity occurs mainly in diastole and is modulated by respiration with inhibition during inspiration (denoted by the upward deflection in the tracing marked *R*) *ECG* = Lead II of the electrocardiogram *ICNA* = inferior cardiac nerve activity *AoP* = aortic pressure

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Heart rate (beats per minute)	150 ± 3	155 ± 5	140 ± 6	148 ± 6	148 ± 6	151 ± 5	153 ± 5
Mean aortic pressure (mm Hg)	103 ± 3	107 ± 16	89 ± 3	93 ± 2	94 ± 2	97 ± 19	98 ± 19†
ICNA (V/5 sec)	15 ± 05	181 ± 07	108 ± 05	107 ± 06	101 ± 06	8.3 ± 06	83 ± 09†
Central venous pressure (mm Hg)	37 ± 03	4 ± 05	4 ± 05	55 ± 05	65 ± 05	85 ± 15	85 ± 15†

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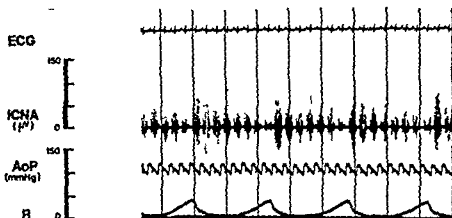


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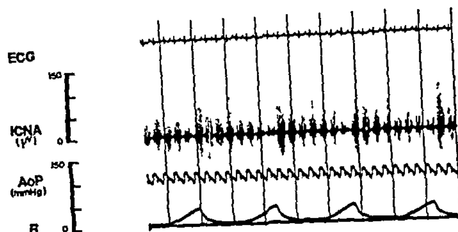


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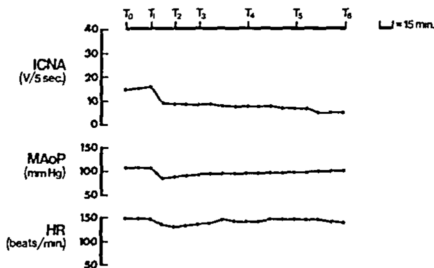


Fig 2 Integrated inferior cardiac nerve activity *(ICNA)* mean aortic pressure *(MAoP)* and heart rate *(HR)* as influenced by occlusion of the circumflex artery in a dog from Group A ICNA remains low as MAoP tend to recover

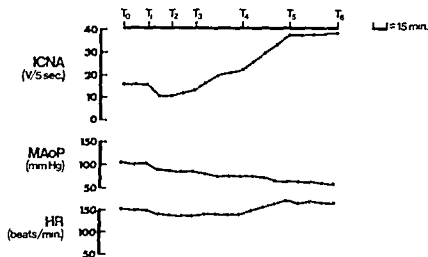


Fig 3 Integrated inferior cardiac nerve activity *(ICNA)* mean aortic pressure *(MAoP)* and heart rate *(HR)* as influenced by occlusion of the circumflex artery in a dog from Group B ICNA increases greatly after the first 30 min period as MAoP continues to fall

preamplifier with a band pass filter of 10 Hz to 10 KHz amplified and displayed with an Electronics for Medicine amplifier and oscilloscope Inferior cardiac nerve activity (ICNA) was quantified by rectification of the phasic signal and integration with an averaging circuit with a 5 second time constant Thus the integrated neural activity was expressed in voltage rise per 5 seconds

Lead II of the ECG, the ICN electroneurogram aortic, central venous and endotracheal pressures were displayed continuously and recorded at regular intervals Mean pressures were obtained by electrical integration Heart rate was computed from the mean of several R R intervals Hematocrit and arterial blood pH and gases were checked every 30 minutes and ventilatory adjustments were made to maintain arterial pH in the range 7 35 to 7 45 Po about 100 mm Hg and Pco_2 between 35 and 45 mm Hg All animals maintained a hematocrit above 40 per cent At the end of the experiment the thoracic sympathetic rami communicantes T_1 to T were cut This maneuver caused rapid and complete cessation of neural discharges indicating that the sampled fibers were postganglionic sympathetic axons

Observations were made for 30 minutes before

Table II Three dogs in which mean aortic pressure progressively declined after occlusion of circumflex artery (Group B)

	Control (T)	Coronary occlusion (T)	*Ischemia* 30 min (T)	1 hr (T)	2 hr (T)	3 hr (T)	4 hr (T)
Heart rate (beats per minute)	150 ± 5	153 ± 3.3	140 ± 0	146 ± 3 3	155 ± 3 3	153 ± 3 3	1[illegible]6 ± 6 6
Mean aortic pressure (mm Hg)	10[illegible] ± 5	107 ± 1 7	86 ± 1 6	91 ± 2.6	87 ± 6[illegible]	80 ± [illegible]6	[illegible] ± 1 4†
ICNA (V/5 sec)	13[illegible] ± 0 2	143 ± 0 8	8 5 ± 1 4	8 8 ± [illegible]6	10 9 ± [illegible]6	17 8 ± 9 8	24 9 ± [illegible]5†
Central venous pressure (mm Hg)	3 5 ± 0 5	3 5 ± 0 5	3 5 ± 0[illegible]	4 ± 0 5	6[illegible] ± 1 5	9 ± 1 5	9 ± 1.5†

P < 0 0 with reference to [illegible] (Student's t test)
† P < 0 001 [illegible] T through T (regression analysis)

and 4 hours after ligation of the circumflex artery Calculations for statistical analysis were made at six time intervals control (T) occlusion (T) 30 minutes (T) 1 hour (T) 2 hours (T) 3 hours (T) and 4 hours of ischemia (T) Each animal served as its own control Mean values ± standard errors for the entire group of dogs were obtained at the same intervals Changes from T to T were analyzed for statistical significance by Student's t test Changes from T through T were first studied for the purpose of establishing a trend by regression analysis (individual parameter vs time) Regression analysis was finally employed to determine the statistical significance of the changes in ICNA with reference to changes in mean aortic pressure

Results

Observations were made in a total of 16 dogs

Background activity of the left inferior cardiac nerve In all animals spontaneous activity of the left ICN consisted of grouped discharges synchronous with the cardiac cycle and modulated by respiration As shown in Fig 1 the intensity of discharge tended to decrease during systole increasing during diastole Superimposed on the cardiac rhythm was a respiratory rhythm that showed an inhibition of sympathetic activity during the inspiratory phase

Effects of coronary occlusion Seven of 16 dogs developed ventricular fibrillation and died within the first 30 minutes of ischemia In these animals that died of ventricular fibrillation the precipitous fall in arterial pressure caused an immediate increase in sympathetic nerve activity

In nine successful experiments which comprise the body of this report observations were made without interruption for a period of 4 hours After coronary occlusion ICNA declined in all experiments to various degrees concomitant with a moderate drop in mean aortic pressure of 2[illegible] ± 3 per cent (P < 0 05) and a comparatively slight reduction in heart rate of 12 ± 3 per cent (P < 0 0[illegible]) The declines in ICNA mean aortic pressure and heart rate lasted 30 minutes in all the dogs in this group After this early phase mean aortic pressure tended to recover in six dogs (P < 0 0[illegible]) whereas it continued to fall in three (P < 0 001) After the first 30 minutes of ischemia ICNA varied in a direction opposite to aortic pressure tending to decline further in the six dogs in which arterial pressure rose (P < 0 0[illegible]) and increasing above baseline (P < 0 001) in the three that went into shock Heart rate did not show a significant trend and respiration was controlled throughout

On the basis of the changes in mean aortic pressure and ICNA the animals were divided into Group A (Table I) in which arterial pressure recovered and Group B (Table II) in which it continued to fall

The course of an experiment from Group A is shown in Fig 2 Reduction in heart rate mean aortic pressure and ICNA followed coronary occlusion Aortic pressure started to rise after 30 minutes of ischemia and continued its recovery trend reaching at T_6 a value that was 16 per cent above T_2 and only 5 6 per cent below control level ICNA remained low throughout In fact it continued to drop and at T_6 it was 42 9 per cent

less than at T and 69 per cent less than at control

The course of an experiment in Group B is shown in Fig 3 The changes during the first 30 minutes of ischemia were similar to those observed in the previous group Subsequently while mean aortic pressure gradually fell to 62 mm Hg (57 9 per cent below control values), ICNA increased reaching at T_6 a value 363 per cent greater than at T_2 and 250 per cent above control

The inverse relationship between ICNA and mean aortic pressure after the first 30 minutes in both subgroups was statistically significant ($P < 0\,005$) All dogs in Group A remained alive for the entire period of observation whereas the three dogs in Group B died as a result of ventricular fibrillation during the fourth hour

Discussion

It is generally agreed that the baroreceptor reflex has a major role in the regulation of sympathetic discharge to the heart [7] The results of these experiments show, however, that acute coronary occlusion produces a reduction of sympathetic drive to the heart that persists for about 30 minutes despite a fall in arterial pressure After this period, ICNA remains attenuated in the animals in which arterial pressure tends to recover whereas it increases whenever severe drops in arterial pressure take place The inverse relationship after the first 30 minutes between ICNA and mean aortic pressure suggests that the cardiocardiac depressor reflex gives way eventually to the baroreceptor control mechanism

Costantin [1] indicated that the duration of the vasodepressor reflex he induced by coronary occlusion was brief waning within 60 seconds Ascanio and associates [5] using an intracoronary injection of hexachlorotetrafluorobutane (Hexa) found the reflex changes of acute myocardial injury to last about 1 hour Using this same method Barrera and associates [3] noted that peripheral vascular resistance decreased significantly for the first half hour after coronary injection tending to recover thereafter Kezdi and associates could by vagotomy raise arterial pressure and cardiac output 3 hours after experimental infarction from coronary embolization with metallic mercury From the latter studies as well as our own it would appear that the effect of acute coronary occlusion on the sympathetic nervous system is long lasting and may, therefore, have significant consequences

At this state of knowledge, one can only speculate on the significance of this reflex The present study shows that reduction of sympathetic drive is an initial response to acute coronary occlusion, which persists only as long as aortic pressure is not greatly reduced This finding suggests that moderate hypotension and bradycardia coupled with reduction of myocardial contractility, are probably desirable effects, in that they tend to reduce the work load and the energy requirement of the ischemic left ventricle Indeed, slower heart rates have been found to be associated with lesser degrees of ischemic injury, [4] whereas stimulation of cardiac sympathetic nerve activity or the administration of sympathomimetic drugs particularly the beta adrenergic agents that stimulate heart rate and contractility have been found to aggravate the effects of ischemia [5, 6] Similarly moderate hypotension without clinical shock not only has not been shown to increase the mortality rate in patients with myocardial infarction but may be beneficial

Although it is appreciated that not all the fibers of the inferior cardiac nerve innervate the myocardium it has been proved that this is the predominant distribution [9, 10] Moreover, our recordings of sympathetic discharge from the left ICN under normal conditions showed a cardiac rhythmicity and were similar to those previously described by Bronk and associates [9] and other investigators [11, 3] Furthermore at the end of each experiment suppression of activity occurred when the preganglionic sympathetic fibers were cut We believe therefore that we were studying sympathetic efferent traffic to the heart No attempt was made however in these experiments to define the afferent pathway of the reflex

In summary our observations suggest that the cardiocardiac depressor reflex produced by coronary artery occlusion may be a homeostatic mechanism that tends to reduce the imbalance between oxygen supply and oxygen demand in the ischemic myocardium and thereby tends to reduce the extent of injury When arterial pressure falls to a critical level however the baroreceptor mechanism designed to increase sympathetic activity overrides this depressor reflex and becomes predominant The clinical implications

of these observations are that moderate brady cardia and hypotension in the early phases of acute myocardial infarction quite likely do not require reversal by pharmacological agents In addition these observations provide some experi mental support for the suggestion that beta receptor blocking agents may be helpful in the treatment of patients with acute myocardial infarction since blocking these receptors would produce effects similar to those resulting from decreased sympathetic traffic

Summary

Sympathetic discharges to the heart were recorded from the left inferior cardiac nerve of 16 dogs Inferior cardiac nerve activity (ICNA) under normal conditions consisted of grouped discharges synchronous with the cardiac cycle and modulated by respiration After ligation of the circumflex branch of the left coronary artery ICNA declined concomitant with a decline in heart rate and mean aortic pressure After 30 minutes when arterial pressure tended to recover toward control values (six dogs) ICNA remained low in contrast when arterial pressure dropped to shock levels (three dogs) ICNA increased When aortic pressure fell precipitously as a result of ventricular fibrillation even during the first 30 minutes of ischemia (seven dogs) ICNA immedi ately increased greatly The results of this study suggest that acute coronary occlusion produces a cardiocardiac depressor reflex with attenuation of sympathetic discharge to the heart This reflex under the experimental conditions studied gives way to the baroreceptor reflex when aortic pres sure drops to critically low levels

REFERENCES

1 Adgey A J Mulholland, H. C., Geddes J S et al. Incidence significance and management of early bradyarrhythmias complicating acute myocardial infarc tion, Lancet 2 1097 1968
2 Grauer L. E Gershen, B J Orlando M M et al. Bradycardia and its complications in the prehospital phase of acute myocardial infarction Am. J Cardiol. 32 607 1973
3 Costantin L. Extracardiac factors contributing to hypo- tension during coronary occlusion Am J Cardiol. 11 705 1963
4 Dokukin A. V Blood pressure and pulse changes in normal and vagotomized animals during acute myocar dial ischemia, Fed Proc. 23 T 582, 1964
5 Ascanio G Barrera F Lautsch, E V et al. Role of reflexes following myocardial necrobiosis, Am. J Physiol. 209 1081 1965
6 Toubes, D B., and Brody M J Inhibition of reflex vasoconstriction after experimental coronary emboliza tion in the dog Circ Res 26 211 1970
7 Glick, G Importance of the carotid sinus baroreceptors in the regulation of myocardial performance J Clin. Invest. 50 1116, 1971
8 Kezdi, P., Kordenat, R. K., and Misra, S N., Reflex inhibitory effects of vagal afferents in experimental myocardial infarction, Am. J Cardiol. 33 853, 1974
9 Paintal, A. S., A study of ventricular pressure receptors and their role in the Bezold reflex, Q J Exp Physiol. 40 348 1955
10 Öberg B., and Thoren, P Studies on left ventricular receptors signalling in non medullated vagal afferents, Acta Physiol. Scand. 85 145 1972.
11. Tennant R., and Wiggers, C J., The effect of coronary occlusion on myocardial contraction Am. J Physiol. 112 351 1935
12. Kolatat, T., Ascanio, G., Tallarida, R. J., et al., Action potentials in the sensory vagus at the time of coronary infarction Am. J Physiol. 213 71 1967
13. Recordati, G., Schwartz, P J., Pagani, M., et al. Activa tion of cardiac vagal receptors during myocardial ischemia Experientia 27 1423, 1971.
14 Thoren, P Left ventricular receptors activated by severe asphyxia and by coronary artery occlusion, Acta Physiol. Scand. 85 455 1972.
15 Oberg, B., and White S Circulatory effects of interrup- tion and stimulation of cardiac vagal afferents, Acta Physiol. Scand 80 383 1970
16. Hanley H. G., Costin J C., and Skinner N S., Jr Differential reflex adjustments in cutaneous and muscu lar vascular beds during experimental coronary artery occlusion, Am. J Cardiol. 27 513 1971
17 Angress, C M., and Binder M J Cardiogenic shock Am. Heart J 54 458 1957
18 Gurman S V., Swenson, E., and Mitchell, R., Mecha nism of cardiogenic shock, Circ Res. 10 746 1962.
19 Levy M N., and Frankel, A. L. Vasomotor responses to acute coronary occlusion in the dog, Am. J Physiol. 172 427 1953
20 Matthes, K. Myocardial shock, *In* CIBA Symposium on Shock, Berlin Heidelberg New York 1962, Springer Verlag p 253.
21 Wegria, R., Frank, C W., Misrahy G A., Wang, H H., et al. Immediate hemodynamic effects of acute coronary artery occlusion, Am. J Physiol. 177 123, 1954.
22 Malliani, A Schwartz, P J., and Zanchetti, A. A sympathetic reflex elicited by experimental coronary occlusion, Am. J Physiol. 217 703, 1969
23 Barrera F., Ascanio G., Lautsch, E. V., et al. Factors in acute hypotension and ventricular fibrillation after cardiac necrosis, Am J Med. Sci. 253 675 1967
24 Redwood D R., Smith, E R., and Epstein S E. Coronary artery occlusion in the conscious dog Effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia, Circulation 46 323 1972.
25 Raab W., Van Lith, P., Lepeschkin E., et al. Catecho- lamine induced myocardial hypoxia in the presence of impaired coronary dilatability independent of external cardiac work, Am. J Cardiol. 9 455 1962.
26 Braunwald E., Covell, J W., Maroko P R., et al. Effects of drugs and of counterpulsation on myocardial oxygen consumption. Observations in the ischemic heart Circulation 41 (Suppl. IV) 220 1969

27 Epstein S E Redwood D R and Smith E R Atropine and acute myocardial infarction Circulation **45** 1273 1972
28 Walinski P Chatterjee K., Forrester, J et al Enhanced left ventricular performance with phentolamine in acute myocardial infarction Am J Cardiol **33** 37 1974
29 Bronk D W Ferguson L K., Margaria R et al The activity of the cardiac sympathetic centers Am J Physiol **117** 237 1936
30 Mizeres N J The anatomy of the autonomic nervous system in the dog Am J Anat **96** 285 1955
31 Downing S E and Siegel J H Baroreceptor and chemoreceptor influences on sympathetic discharge to the heart Am J Physiol **204** 471 1963
32 Ninomiya I Nisimaru N., and Irisawa H Sympathetic nerve activity to the spleen kidney and heart in response to baroreceptor input Am J Physiol **221** 1346, 1971

Uncommon cardiovascular manifestations and high catecholamine levels due to ' black widow' bite

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Black widow s bite is known to produce neuro logical manifestations in animals and in man [2] profuse perspiration and salivation convulsions and cardiovascular collapse are the commonest Hypertension and bradycardia are less frequent

We describe here a patient after a black widow spider bite who developed a very unusual cardiovascular complication atrial fibrillation and labile blood pressure associated with high levels of urinary vanillyl mandelic acid (VMA) This phenomenon has not yet been described in relation to the spider s bite

Case report

A 25-year-old Bedouin man was admitted to the Medical Department A on May 28 1975 1 hour after being bitten by a black widow spider *Lactrodectus m. tredecimguttatus* On admission he looked very ill covered by profuse cold perspira tion Temperature was 37 C blood pressure was unstable varying between 120 and 240 systolic and 80 and 140 diastolic pulse was 110 weak and regular Physical examination was otherwise normal except for tenderness in the right leg around *the site of the bite*

The erythrocyte sedimentation rate (ESR) was 2/3 the hemoglobin (Hgb) was 18 3 Gm per 100 ml. *the hematocrit* (Hct) was 52 per cent the white blood count (WBC) was 13 100 with a normal differential and thrombocytes, 160 000 Results of tests of urine blood urea creatinine Cl, Na K liver function transaminase creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) were normal An electrocar diogram (ECG) showed sinus tachycardia A chest x ray was normal.

Intravenous therapy with 10 per cent calcium gluconate and 40 units of ACTH in 5 per cent glucose was started at the time of admission and stopped at 48 hours as the patient was completely asymptomatic Then 72 hours after admission the patient felt sudden precordial pain palpitations and profuse perspiration The blood pressure became very un table and the pulse was irregular and weak An ECG showed fast atrial fibrillation (180 to 210) Urine samples for VMA determina tions were taken before therapy with propranolol (5 mg intravenously) under monitoring Dramatic stabilization of blood pressure followed but no change in the cardiac arrhythmia occurred. After 2 hours, two intravenous doses of 1 mg of digoxin were injected at a 30 minute interval without any result Two hours later 1 mg of oxprenol hydrochloride was given intravenously and at the end of the injection the heart rate became regular and an ECG showed a 100 sinus rhythm without any pathological changes.

Oxprenol hydrochloride was continued at 20 mg by mouth three times a day Pretreatment urine VMA was 6 gamma per milligram of creatinine (normal 0.5 to 3 5 gamma per milli gram of creatinine) The patient was discharged in an excel lent condition 6 days after admission without medication A *follow up* ECG was normal and no changes in serum transam inases CPK or LDH levels were observed

Discussion

In previous publications we found that cardio vascular changes after yellow scorpion sting were related to increase of pressor amines due to the effect of the venom on the autonomic system [4] Therapy with beta blockers in a patient with severe cardiovascular manifestations like unsta ble blood pressure and S T changes had a dramatic effect which supported our statement [3] The neurological damage after black widow bite is probably the result of the venom on the autonomic system whereas cardiovascular mani festations and arrhythmias are rare

The demonstration of high levels of urinary catecholamines during the cardiovascular distur bance has not been described before and has therapeutic implications We suggest that beta blockers have a beneficial effect in the control of cardiovascular disorders caused by a black widow bite as seen in our patient

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REFERENCES

1 Minton S A Venom diseases Springfield Ill, 1974 Charles C Thomas Publisher p 44

2 Lefkowitz M Kadish H and Stern J Spider bite *Dapim Refuim* **21** *28 1962*

3 Herman G A The determination of urinary 3 methoxy 4 hydroxymandelic (vanilmandelic) acid by means of electrophoresis with cellulose acetate membrane Am J Clin Pathol **41** 373 1964

4 Gueron M and Weitzman S Catecholamines an myocardial damage in scorpion sting AM HEART J **75** 715 1968

5 Sclarowsky S and Levine M The use of alfa and bet *blockers in a case of yellow scorpion sting* with seve cardiovascular manifestations Harefuah **77** 521 1969

Complete heart block as a cause of syncope in asymmetric septal hypertrophy

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Intraventricular conduction disturbances have been noted in association with asymmetric septal hypertrophy (ASH) but reports of high grade heart block rarely appear The following case is that of a 35 year old man with ASH who presented with syncope the basis for which was found to be complete atrioventricular (A V) block

Case report

A 35 year old Portuguese man presented to Rhode Island Hospital because of multiple syncopal attacks first noted in the 30 minutes prior to admission The patient was well until 20 years of age when he was hospitalized for a swollen left knee and fever A heart murmur was heard and he was diagnosed as having acute rheumatic fever Following an uneventful recovery he resumed a physically active life In the ? years prior to admission he had experienced infrequent nonexertional, sharp precordial chest pains and momentary episodes of light headedness Electrocardiograms (ECG s) taken in 1967 and 1973 were consistent with progressive left ventricular hypertrophy

Sixteen of the patient s 23 siblings died before the age of 8 months of unknown causes and seven are living One brother has been hospitalized for syncope and one has recently become symptomatic due to ASH There was no personal or family history of seizure disorder

On the day of admission the patient experienced two syncopal episodes while gardening ECG telemetry during transit to the hospital showed dropped beats preceded by constant P R and R R intervals consistent with a Mobitz Type II A V block Shortly after arrival in the emergency room the patient developed complete heart block with no escape rhythm and lost consciousness. Following cardiopulmonary resuscitation and the institution of ventricular pacing with a balloon tipped bipolar pacing electrode the patient regained consciousness

Physical examination disclosed a blood pressure of 1?0/80 mm Hg and a regular paced pulse of 70 beats per minute Peripheral pulses were of normal quality The lungs and abdomen were unremarkable A grade 2/6 mid systolic high pitched murmur did not change with Valsalva maneuver handgrip or upright position After establishment of A V synchronous pacing the murmur became louder in the upright position

An echocardiogram demonstrated abnormal systolic anterior motion (SAM) of the anterior mitral valve leaflet increased septal to posterior left ventricular wall thickness (ratio 1 3/1 0) decreased septal motion diminished mitral E to F slope and early aortic valve closure These echocardiographic findings are consistent with the diagnosis of ASH (see Fig 1)

Cardiac catheterization revealed no resting gradient between the apex of the left ventricle (LV) and the LV outflow tract or aorta There was a provocable LV aortic systolic gradient as great as ? mm Hg following premature ventricular contractions during an isoproterenol infusion (see Fig 2) A right anterior oblique ventriculogram showed a small slit like end systolic LV chamber (see Fig 3) Coronary arteriography was normal To assess the importance of the timing of atrial contraction in relation to cardiac output A V sequential pacing was performed Cardiac output by dye dilution method was ?1 L per minute during ventricular pacing and 7.8 L per minute with A V sequential pacing at an identical rate

A His bundle ECG showed His spikes after atrial deflections with normal A H intervals consistent with A V block below the His bundle (see Fig 4) During the subsequent hospitalization occasional conducted beats were noted in which left bundle branch block was present

Systolic time intervals (STI) showed variable pre-ejection period to LV ejection time ratios (PEP/LVET) dependent upon the PR intervals during A V dissociation A PR interval of 0.26 second produced the optimal PEP/LVET ratio (0 313)

A sequential A V pacemaker (Cordis Omni Atriocor) was implanted with endocardial leads The atrial sensing electrode was placed in the coronary sinus and the stimulating electrode in the right ventricular apex There was a preset heart rate of 70 and a PR interval of 0 18 second The patient made an

From th D vis of B logi al d Medical Science Brown Uni sit nd Division of Card ol gy Rh de I I nd Hosp tal Pro dence R I

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Takayasu's arteritis Clinical study of 107 cases

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Few entities in the medical literature have been labeled with as many eponyms as has Takayasu's arteritis (TA) It has been known as pulseless disease, aortic arch syndrome young female arteritis idiopathic aortitis, reversed coarctation Martorell syndrome and numerous others[1-5] Confusion has arisen because many of the above terms for the condition have previously been considered as separate disease entities

Nonspecific arteritis was first described by Savory[6] and Kussmaul in 1856 In 1908 Takayasu[7] noted the ocular changes of the disease in a 21 year old woman These consisted of a peculiar capillary flush in the ocular fundi a wreathlike arteriovenous anastomosis around the papillae, and blindness due to cataracts Subsequently, in the discussion of this case,[7] Onishi and Kagoshima pointed out in two cases with similar ocular manifestations the absence of pulses in the arms In 1948 Shimizu and Sano[1] detailed the clinical features of this disorder which in 1954 was termed Takayasu's arteritis

Initially, it was thought that the arteritic process was limited to the aortic arch and its branches Subsequent clinical and pathologic studies have demonstrated that the arteritis is not confined to these areas Ueno and associates[8] have defined three varieties of TA In Type I (Shimizu Sano[1, 2]) the involvement is localized to the aortic arch and its branches In Type II also called atypical coarctation of the aorta or Kimoto[9] variety the lesions involve the thoracic descending aorta and the abdominal aorta without involvement of the arch Type III or mixed variety,[10] contains features of both We have recently suggested an additional variant (Type IV) which may involve any of the features of Types I, II, or III and in addition involves the pulmonary artery[11] (Fig 1) Although many patients with TA have been studied and its clinical and pathologic features have been the subject of numerous reports, its etiology has not been elucidated[1-18] In this report we describe the clinical experience derived from 107 cases of TA studied at the National Institute of Cardiology of Mexico

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Materials and methods

A retrospective review was done of 107 charts of patients with TA studied during a 19 year period up to May 1974 The diagnosis of TA was established by clinical and angiocardiographic data in all cases In addition arterial biopsy or autopsy confirmation was obtained in 28 per cent of the cases The patients were separated into four categories according to the classification of Ueno and associates[8] as previously modified[11] Localization of the arterial lesions by aortography was performed in all cases and pulmonary angiography was carried out in 35 cases Patients not included in this study were those with the age of onset over of 35 (six cases) to avoid with atherosclerotic vascular disease

Results

Ninety patients (84 per cent) were female and 17 (16 per cent) were male Most patients ages ranged from 11 to 30 years (80 per cent) The youngest currently is 4 years old and the oldest is

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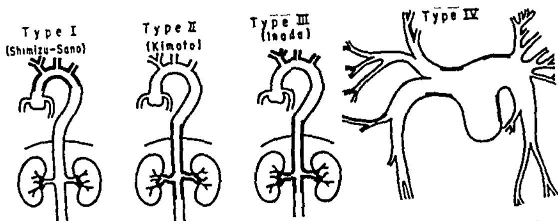


Fig. 1. Clinical classification of TA as proposed by Ueno and associates and modified by us. The thicker dash lines represent the areas of involvement.

currently 45. In 77 per cent of the patients the age of onset was between 10 and 20 years. This clinical time from the onset of symptoms was from 2 to 11 years in 78 per cent of the patients (shortest time 1 month, longest 24 years). The clinical manifestations of the 107 cases are shown in Table I. In the young, the onset is usually acute with 67 per cent of the patients under the age of 15 presenting for the first time in heart failure. We have termed this the "first acute phase" of the arteritis. This is followed by a long period of chronicity with intermittent exacerbations and gradual deterioration. Older subjects tend to present without the first acute phase of the arteritis but the subsequent chronic course is similar. The laboratory findings are shown in Table II and the radiologic and electrocardiographic (ECG) data in Table III. The topography of the arterial lesions is tabulated in Table IV. Nine patients (8 per cent) had Type I arteritis, 12 (11 per cent) had Type II, 70 (65 per cent) had Type III, and 16 (45 per cent) had Type IV (16/35).

The contrast medium revealed one or more of the following: irregular internal surface of the vessel wall, stenosis, poststenotic dilatation, occlusion of the proximal portions of the branches of the aorta, and saccular aneurysms (Figs. 2 and 3). Collateral circulation was demonstrated in 94 per cent of the aortographic studies. Severe aortic coarctation was present in 29 per cent of cases. Four (3 per cent) patients developed occlusion of the femoral artery after aortography and required surgery but there was no procedural or operative death.

The diseases occurring concomitantly with TA are shown in Table V. Standard treatment was prescribed for heart failure and arterial hypertension. Corticosteroids administered to eight patients did not produce any clinical remissions in six but in two cases general symptoms (anorexia and asthenia) disappeared. Fifteen patients received medical treatment for tuberculous adenopathy. None of these was in the acute phase of TA and none showed a change in the clinical course of the disease. Anticoagulant treatment was used when indicated and not routinely. Twenty-two patients were submitted to surgery for the relief of hypertension. In 13 cases nephrectomy and in five other cases bypass surgery was carried out after angiographic evidence of unilateral renal lesions was obtained. In five cases remission of the hypertension was observed but in the remainder there was no change. Arterial bypass was performed in nine cases and the results are shown in Table VI. The over-all mortality rate directly related to TA was 14.0 per cent and the causes of death are shown in Table VII.

Discussion

Takayasu's arteritis is a nonspecific inflammatory process of unknown etiology affecting segmentally the aorta and its main branches.[3, 4, 5] The end result of the marked fibrosis and thickening of the arterial wall is usually a constriction or occlusion and occasionally a saccular aneurysm.[1] TA has been recognized in many countries and on almost all continents.[2, 1] The clinical picture as presented in these reports from various countries has differed to some extent and each group has emphasized either clinical or pathologic

Review

Takayasu's arteritis Clinical study of 107 cases

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Ninety patients (84 per cent) were female and 17 (16 per cent) were male Most patients ages ranged from 11 to 30 years (80 per cent) The youngest currently is 4 years old and the oldest is

Table III Radiologic and ECG findings

	No. of cases	Per cent
A *Radiologic*		
Normal x ray	42	39
Cardiothoracic index		
50-55%	29	27
56-60%	26	24
61-65%	9	8
> 66%	1	0.9
Pleural effusion	6	5
Pulmonary artery hypertension	8	7
Tuberculous lesions	?	1
Calcifications		
Aortic	17	15
Aortic valve	1	0.9
Hilar lymph nodes	61	57
Abdominal lymph nodes	2	1
Notching of the ribs	8	7
B *Electrocardiogram*		
Normal	23	21
Abnormal	84	78
Left atrial enlargement	11	10
Right ventricular hypertrophy	5	4
Left ventricular hypertrophy	3	68
Right bundle branch block	3	2
Left bundle branch block	5	4
Left anterior fascicular block	3	2
Atrial flutter	1	0.9
Myocardial infarction	9	8

Observed only in Type IV arteritis

diminishes the natural clinical course of TA is to chronicity with gradual deterioration however short periods of acute flareups lasting 1 to 2 weeks are seen in the course of the disease

As did to Nakao and associates, we found that the most frequent variety of TA involved the supra aortic trunks and the abdominal aorta in 65 per cent of cases (Type III). Type IV with pulmonary artery involvement in addition was the second most frequent. It is important to recognize these variations for diagnostic and therapeutic reasons. The only discriminating clinical features among the four types were the absence of arterial hypertension in patients with Type I arteritis and the high incidence (50 per cent) of right heart strain in Type IV arteritis (8/16).

The cardiovascular and neurologic symptoms in the present study were usually present at the same time. The predominant cardiovascular symptoms were dyspnea, raised blood pressure (usually diastolic BP < 140 mm Hg), vascular bruits, and the classical finding of reduction amplitude of peripheral pulses in 96 per cent of cases. Normal or even wide pulse amplitude was found in patients with mild degrees of arteritis and in two patients with aortic regurgitation (a clinical complication that could mask the disease). Most of the patients had arterial obstruction but only a few complained of ischemic pain, apparently related to the fact that artery obstruction occurred gradually and with parallel development of collateral circulation. The second important cardiovascular sign was systolic vascular bruits resulting from endothelial irregularity, stenosis, and collateral circulation whose detection and location are described elsewhere.

Table IV Topography of the arterial lesions in 107 patients with Takayasu's arteritis (from angiography and necropsy findings)

Artery	Right	Left	Bilateral	Total	Per cent
Ascending aorta and arch	–	–	–	29	27
Descending aorta	–	–	–	72	67
Subclavian	14	27	50	91	85
Carotid	8	20	20	48	44
Brachiocephalic trunk	–	–	–	17	15
Coronary	2	8	–	10	9
Vertebral	9	5	7	21	19
Pulmonary	10	4	2	16	14
Splenic	–	–	–	3	2
Mesenteric	–	–	–	16	14
Renal	19	17	31	67	62
Iliac	1	6	11	18	16
Femoral	1	2	1	4	3
Brachial	3	1	2	6	5
Tibial	2	1	2	5	4

Table V Takayasu's arteritis and related diseases

Disease	No. of cases	Per cent
Bazin's erythema induratum	28	26
Tuberculous adenopathy	15	14
Previous history of tuberculous adenopathy	8	7
Pulmonary tuberculosis	2	1
Tuberculosis of the hip	1	0.9
Diabetes mellitus	5	4
Bronchial asthma	1	0.9
Thyrotoxicosis	1	0.9
Total number of cases	61	57.0

Forty-eight per cent of the patients had previous history of active tuberculosis.

Table I Clinical features of patients with Takayasu's arteritis

		No of cases	*Per cent*
A	*General symptoms*	84	78
	Asthenia	60	56
	Weight loss (< 4 Kg)	24	22
	Fever	20	18
B	*Cardiovascular*		
	Dyspnea on exertion	78	72
	Paroxysmal dyspnea	20	18
	Palpitations	47	43
	Angina pectoris	12	11
	Intermittent claudication	32	29
	Hemoptysis	5	4
	Pulse deficit	103	96
	Vascular bruits	101	94
	Valvular bruits		
	Mitral regurgitation	6	5
	Aortic regurgitation	8	7
	Pericardial rub	3	2
	Heart failure		
	Left side	30	28
	Right side*	8	7
	High blood pressure †	78	72
	Diastolic < 140 mm Hg		79
	Diastolic > 140 mm Hg		21
C	*Neurologic*		
	Headaches	61	57
	Syncope	14	13
	Hemiplegia	8	7
	Paraplegia	1	0 9
	Visual disturbances	9	8
	Hypertensive encephalopathy	4	3
	Abnormal fundi‡	44	41
	Grade I	26	24
	Grade II	9	8
	Grade III	3	2
	Grade IV	4	3
	Cataract	2	1
	Vascular neoformations	2	1
D	*Abdominal*		
	Vomiting	21	19
	Diarrhea	10	10
	Pain	8	7
E	*Miscellaneous*		
	Arthralgias	57	53
	Palpable cervical nodes	28	26
	Irregularity of menses	3	2

*Right sided failure observed only in type IV arteritis
†Not observed in type I arteritis
‡Keith Wagner classification of fundi

Table II Laboratory findings

		No of cases	*Per cent*
A	*C B C*		
	R B C < 4 000 000/mm³ (hypochromic or normochromic normocytic)	27	25
	Increased erythrocyte sedimentation rate	89	83
	Leukocyte count (10 000 to 23 000/mm³)	11	10
B	*Blood urea nitrogen (> 60 mg per 100)*	18	16
	Creatinine (> 2 mg per 100 ML)	5	4
	Urinalysis		
	Abnormal	41	38
	Albuminuria	30	28
	Cylinduria	10	9
	Hematuria	3	2
C	*Lipoproteins*		
	Normal	75	70
	Increased Type IIa	3	2
	Increased Type IV	3	2
	C reactive protein > 2+	25	23
	Antistreptolysin O titer > 300	26	24
	Positive rheumatoid factor	5	4
	Positive VDRL	1	0 9
	Positive Mantoux (2 U T)	87	81
	Positive antinuclear antibodies	7	6
	Positive LE cell	3	2
	Increased euglobulins	2	1
	Increased gamma globulins	37	34
	Positive arterial biopsy	15/42	35

Frederickson classification

aspects The arteritis has been observed in children from 3 to 14 years[34,36] and they represent 7 5 per cent of the patients with TA The disease occurs predominantly in females (8 5 1)[18] with age of onset between 10 and 20 years Our observations suggest that in the young, TA is characterized by the sudden onset of constitutional symptoms (fever anorexia weight loss), joint pain (s), symptoms and signs of a local circulatory deficit, high blood pressure and elevated erythrocyte sedimentation rate This clinical picture (first acute inflammatory phase) is observed in about half the cases and may disappear partly or completely in about 3 months time, only to reappear in a chronic phase some months later Some patients already have advanced arterial obstruction and evidence of collateral circulation when they first develop symptoms These patients have prominent cardiovascular and neurologic symptoms Although it has been stated in the past[4] that cardiovascular involvement plays a minor role in the disease process, the data from this study demonstrate that the cardiovascular system may be involved at any point in the illness When the acute inflammatory phase



Fig 4 Patient with Type III arteritis Involvement of the abdominal aorta and renal arteries with old thrombosis of the right renal artery



Fig 5 The right coronary artery is opened to show a saccular aneurysm with fresh thrombosis.

nary artery at necropsy was disproportionate to angiographic studies[1] Clinical pathologic correlations have shown that minor lesions may be overlooked by angiography[1, 35] Contrary to the findings of other authors our renal arterial grafts tended to occlude and we feel there is no place for them

The possibility of TA was strongly suggested in young women with high blood pressure reduction in arterial pulses (especially if in the right arm) and vascular bruits Heart failure in TA is generally regarded as a consequence of systemic arterial involvement hypertension and in some cases pulmonary vascular involvement[1, 3, 7] It was previously thought to be the result of direct myocardial damage but the pathologic findings in the heart are nonspecific and related to heart failure and systemic and pulmonary hypertension[8, 1, 12, 36, 37, 45] Symptoms of coronary artery involvement rarely occur in the absence of other manifestations of TA and coronary involvement is itself a rare complica

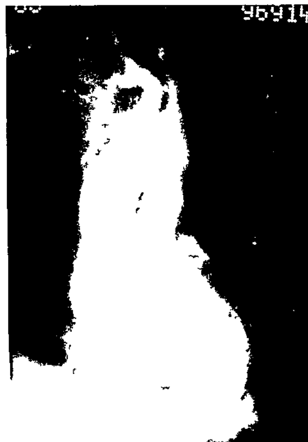


Fig 2 Aortogram of patient with Type I arteritis There is no filling of the right and left subclavian arteries The left carotid is narrowed



Fig 3 Aortogram of patient with Type III arteritis Severe coarctation of the descending thoracic and abdominal aorta A post stenotic dilatation is shown

Table VI Result of the arterial bypass of nine patients with Takayasu s arteritis

From	*To*	*No of cases*	*NP**	*P*
Descending thoracic aorta	Abdominal	2	2	0
Abdominal aorta	External iliac	1	0	1
Aortic arch	Carotid	1	0	1
Abdominal aorta	Renal	5	4	1
Total number of cases		9	6	3

NP Not patent P patent > 2 years

Table VII Cause of death in 16 patients with Takayasu s arteritis

	Types of TA				*Total no of cases*	*Per cent*
	I	*II*	*III*	*IV*		
Heart failure	0	0	6	2	8	7
Renal failure	0	1	2	0	3	2
Myocardial infarction	0	0	2	0	2	1
Cerebral hemorrhage	0	0	1	0	1	0 9
Rupture of subclavian aneurysm	1	0	0	0	1	0 9
Peritonitis from perforation of gastric ulcers	0	1	0	0	1	0 9
Total number of cases	1	2	11	2	16	14

Arterial hypertension was present in 72 per cent of our patients mainly resulting from involvement of the renal arteries which occurred in 62 per cent of cases as demonstrated by aortography and necropsy studies[11, 3, 4] (Fig 4) Old and fresh thrombosis of the renal arteries was a common finding in kidneys obtained at surgery and at necropsy both in our series and in others[1, 3] In a few cases recanalization of the thrombi occurred but development of renal ischemia was the rule The arterial hypertension was generally of moderate degree and only in a few cases was it severe similar to the findings of others[1, 39, 4] Usually it can be managed with medical treatment Surgery was rarely indicated and nephrectomy was not effective in 50 per cent of the patients who had unilateral renal artery lesions on renal arteriography Failure of blood pressure to return to normal in some cases may have been due to bilateral involvement of the renal arteries not shown by angiography Similarly in some cases involvement of the pulmo

of concomitant clinical manifestations of syphilis and positive anticomplementary Wassermann test in patients with TA[6] Furthermore when aortic calcification is found in TA it usually involves the descending and not the ascending aorta[6] as in syphilitic aortitis Treponema staining of the lesions in arterial walls has also been shown to be negative For some authors all these negative features do not rule out a syphilitic origin of TA but we do not feel it to be the case Recent reports from the tropics suggest a possible role of an unidentified nematode with arterial tropism mainly affecting children and young adults[1] Because nematodes are usually confined to the tropics this would not explain the world wide incidence of TA Nematodes however may be a cause of some cases of arteritis observed in the tropics[2, 33]

The role of tuberculosis in TA was pointed out in 1948 by Shimizu and Sano They considered this possibility on the basis of the presence of Langhans giant cell granulomas resembling morphologically tuberculous lesions Many authors have shown the coexistence of pulmonary or extrapulmonary tuberculous foci in TA especially in juxta arterial and para aortic lymph nodes[1, 2, 6] In these series we have observed that 48 per cent of the patients had a previous tuberculous infection such as tuberculous adenopathy pulmonary tuberculosis and Bazin's erythema induratum (Table V) Positive PPD reaction was found in 81 per cent as compared with 66 per cent in the normal Mexican population[4] with a Grade IV skin reaction in some patients The intradermal reactions with specific antigens of *Mycobacterium kansasii* (84 per cent) and avium (78 per cent) are also more commonly positive in TA than in the average population without arteritis (11 to 15 per cent) Some investigators[7] have found that when *M tuberculosis* is inoculated into the subadventitial layer of the rabbit carotid artery changes similar but not identical to those of TA are produced also the disease pattern was closer to that of TA when the rabbits were previously sensitized These clinical observations and experimental work suggested that tuberculosis may play an important role in the etiology of TA

Several investigators have linked TA to immunologic disorders and have postulated that an autoimmunologic mechanism is in operation[7, 34, 6, 7] This hypothesis is supported by certain laboratory findings high gamma globulins circulating antiaorta antibodies the failure to detect any etiologic agent in the lesions of the arterial wall and the systemic arterial nature of the disease (pulmonary and aortic involvement)[11, 12, 15, 17] Although antiaorta antibodies have been found in the serum of patients with this condition there is no definitive evidence at present that these antibodies are the direct cause of TA[7, 8] This mechanism is not against a tuberculous etiology in which the immunologic mechanism is delayed hypersensitivity We favor the hypothesis that antigenic fractions of the mycobacteria may result in toxic injury to the vessel wall as has been demonstrated experimentally in other forms of arteritis[8]

Most of the difficulties in determining the cause of the disease arise because[1, 27] the pathologic observations are usually made in cicatricial or chronic states and only a few during active arteritis Further experimental work should be encouraged in TA in order to find the cause of the disease

The response to treatment for heart failure and hypertension is usually good[1] Some authors have obtained remarkable clinical remissions with corticosteroids We have obtained remissions of systemic symptoms in only two of eight cases At the present time this therapy needs further evaluation and we feel there are not enough clinical and experimental data to justify the routine use of corticosteroids Medical treatment for tuberculosis is indicated only when active tuberculosis is found and is not justified in all cases until its exact role in TA is well established Surgery should be performed preferably during the chronic phase and should be carefully evaluated in each case and employed only when medical treatment has failed to control severe arterial hypertension or vascular insufficiency or when the possibility of rupture of an aneurysm exists

Summary and conclusion

The clinical experience derived from the retrospective study of 107 cases of TA over a 19 year period is presented The disease predominated in females (8 5 1) with age of onset usually less than 20 years In half of the cases an acute inflammatory phase was observed characterized mainly by systemic and cardiovascular symptoms Subsequently the natural course of TA was toward

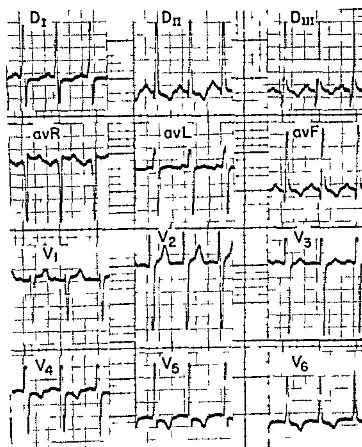


Fig 6 ECG Left ventricular hypertrophy and old inferior myocardial infarction are shown In the precordial leads the sensitivity has been reduced by 50 per cent

tion [1] (Figs 5 and 6) There is only one reported case of TA with granulomatous myocarditis and pericarditis [51]

The neurologic symptoms result from arterial hypertension or cerebral or spinal cord ischemia [1, 4] Variations among neurologic symptoms can be explained on the basis of irregular distribution of arterial lesions and of the development of collateral circulation Encephalomalacia or cerebral hemorrhage can sometimes be observed and are the cause of both permanent signs and also transient neurologic deficits resulting from transient vascular impairment [4, 5, 11, 14, 18, 3, 5, 31] Visual disturbances are mainly related to hypertension [1] In some aortograms lesions were observed at the origins of the mesenteric arteries Gastrointestinal symptoms may be related to these lesions The clinical picture of TA may lead to diagnostic confusion [37] mainly with aortic coarctation [41, 42, 44] but the presence of widespread arterial lesions—predominantly renal involvement and heart failure—after the age of 5 years is more suggestive of TA [4, 54, 55] Absolute confirmation of the diagnosis was given by the arterial biopsy which was positive in only 35 per cent of the present series A negative biopsy did not rule out TA, particularly if other forms of arteritis, such as giant cell syphilitic, bacterial, etc , were excluded In our experience TA was the most common type arteritis

The etiology of TA has still not been clarified 100 years after its original description [6] Attempts have been made to relate it to rheumatic fever [1] and rheumatoid arthritis [43, 56, 5] syphilis [1] to autoimmune disorders (such as systemic lupus erythematosus, polymyositis, scleroderma),[13, 49, 56, 58, 3] ankylosing spondylitis [6] giant cell arteritis,[12, 61] tuberculosis [1, 11, 1, 4, 5, 36] and, more recently nematodes [53] A possible relationship between TA and rheumatoid arthritis has been suspected by several authors [43, 56, 5, 6, 63] as joint pain, iritis sclerokeratitis and positive rheumatoid factor have been found in cases of TA Aortic lesions histologically similar to those of TA have also been found in cases of rheumatoid arthritis, especially in the presence of rheumatoid nodules although rheumatoid nodules are not specific for rheumatoid arthritis and have been observed in lupus erythematosus, granuloma annulare, and diabetes [1] In these series some patients showed arthralgia and weakly positive rheumatoid factor but there was no correlation between the presence of arthritis and a positive rheumatoid factor High titers of antistreptolysin O and positive C reactive protein were found in 23 per cent of the present cases this could be due to previous contact with streptococcus, but on admission no clinical evidence of active rheumatic fever was found and the titers failed to fall subsequently On the other hand the lesions of rheumatic arteritis occur at different sites from those of TA and in particular Aschoff bodies have never been demonstrated in the heart [1]

Other authors have related giant cell arteritis to TA [12, 61, 65, 6] Giant cell arteritis predominantly involves medium sized muscular arteries but is also known to affect the aorta Giant cell arteritis however occurs more frequently in persons older than 50 years and its histologic picture is characterized by the presence of many giant cells and eosinophils [1] On this basis therefore this disease is likely to be a separate entity A possible syphilitic nature of TA has been considered for several years mainly because of the histologic observation that the cicatrization of TA resembles that of syphilitic aortitis [1] On the other hand it is not frequent to find a previous history

Alvarez J J Arteritis inespecifica en la nınez Arch Inst Cardiol Mex 39 1 1969
35 González C J Villavicencio L Molina B and Bessudo J Non specific obliterative aortitis in children Ann Thorac Surg 4 193 1967
36 Lupi H E Contreras R Espino-Vela J Sánchez Torres G and Horwitz S Arteritis inespecifica en la ninez Observaciones clinicas y anatomopathologicas Arch Inst Cardiol Mex 42 4 7 19 2
3 Brownnell W H The many faces of pulseless disease Dis Chest 43 433 1963
38 Sánchez T G Compresión arterial Una maniobra clinica para localizar algunos soplos vasculares, Arch Inst Cardiol Mex 41 531 1971
39 Ask Upmark E On the pathogenesis of hypertension in Takayasu's syndrome Acta Med Scand 169 467 1961
40 Martorell, F Maladie de Takayasu et syndrome de Martorell Folia Angiol 20 124 1972
41 Inada K and Kawahara T Atypical coarctation of the aorta Its genesis and mechanism of hypertension Jap Circ J 27 729 1963
42 Sánchez Torres G Zamora C Melcom G and Alvarez A Coartacion atípica de la aorta por arteritis inespecifica Arch Inst Cardiol Mex 40 602, 1970
43 Austen G N and Shaw R S Surgical treatment of pulseless disease N Eng J Med 270 1228 1964
44 Sunada T and Inada K Atypical coarctation with a special reference to the genesis Jap Circ J 30 ‹? 1966
45 Ask Upmark E On the pulseless disease outside of Japan Acta Med Scand 149 161 1954
46 Judge R D Currier R D Gracie W A and Figley M M Takayasu's arteritis and the aortic arch syndrome Am J Med 32 379 1962
4 Birke G Ejrup B and Olhagen B Pulseless disease Clinical analysis of ten cases Angiology 8 433 1957
48 Heggtveit H A Hennigar G R and Morrione T G Panaortitis Am J Pathol 42 151 1963
49 McKusick V A Form of vascular disease relatively frequent in the Orient Am Heart J 63 57 1962
50 Rosen N and Gaton E Takayasu's arteritis of coronary arteries Arch Pathol 94 225 1972
51 Roberts W C and Wibin E A Idiopathic panaortitis supra aortic arteritis granulomatous myocarditis and pericarditis Am J Med 41 453 1966
52 Lupi H E and Sánchez Torres G Arteritis inespecifica y paraplejia intermitente Arch Inst Cardiol Mex 42 131 1972
53 Munoz N and Correa P Arteritis of the aorta and its major branches Am Heart J 80 319 1970
54 Shapiro M J Coarctation of the abdominal aorta Am J Cardiol 4 547 1959
55 Robicsek F Sanger P W and Daugherty H K Coarctation of the abdominal aorta diagnosed by aortography Ann Surg 162 227 1965
56 Ikeda M Immunologic studies on Takayasu's arteritis Jap Circ J 30 87 1966
57 Plachecka M Kopec M and Kowalska M Rheumatoid factor in Takayashu syndrome Acta Rheum Scand 12 79 1966
58 Hirsch M S Aikat B K and Basu A K Takyasu's arteritis Report of five cases with immunologic studies Johns Hopkins Med J 115 29 1964
59 Riehl J and Brown W J Takayasu's arteritis An auto-immune disease Arch Neurol (Chicago) 12 92 1965
60 Ansell B M Bywaters E G L and Doniack I The aortic lesion of ankylosing spondylitis Br Heart J 20 507 1958
61 Contreras R Castaneda H I and Quijano Pitman F Aneurisma aortico por arteritis de celulas gigantes Arch Int Cardiol Mex 35 818 1965
62 Sanching H and Welin G Aortic arch syndrome with special reference to rheumatoid arteritis, Acta Med Scand 170 1 1961
63 Falicov R E and Cooney D F Takayasu's arteritis and rheumatoid arthritis Arch Intern Med (Chicago) 114 594 1964
64 Kulka J P The pathogenesis of rheumatoid arthritis, J Chron Dis 10 388 1959
65 Waaler E and Milde E J Is there a relationship between giant cell" arteritis with polymyalgia rheumatica and rheumatoid arthritis? Acta Pathol Microbiol Scand 72 347 1968
66 Shimada S Sugiyama Y, and Ogawa I Giant cell arteritis Report of a case Acta Med Biol 4 67 1956
67 Lupi H E, Horwitz S and Sánchez Torres, G Calcifications in Takayasu's arteritis Vasc Surg 7 259 19 3
68 Lupi H E Sánchez Torres G and Castillo P U Reactividad cutanea al PPD a los antígenos de myco-bacterias atípicas (kansasu, avium y fortuitum) en pacientes con arteritis inespecifica Arch Inst Cardiol Mex 42 717 1972
69 Sánchez Torres, G Contreras, R, Barroso M B Zajarías, S Davila R and Lupi, H E Adenitis tuberculosa y arteritis de Takayasu Arch Inst Cardiol Mex 42 663 19 2
70 Sánchez Torres G Arteritis inespecifica y enfermedad tuberculosa Aspectos clinicos Arch Inst Cardiol Mex 42 717 1972
71 Sen P K Kinare S G Kelkar M D and Nanivadekar S A Non-specific stenosing arteritis of the aorta and its branches A study of a possible etiology Mount Sinai J Med 39 221 1972
72 Sánchez Torres G and Barroso M B Eritema nodoso y eritema indurado de Bazin su relacion con las arteritis inespecificas Arch Inst Cardiol Mex 41 414 1971
73 Thuffault C R, and Smith S P Extrapulmonary tuberculosis with erythema nodosum and occlusive arterial disease Can Med Assoc J 95 2 5 1966
74 Takezawa H Sakakura M Kokan Y, and Hamaguchi, Y Report of two cases of Takayasu's disease complicated with tuberculoid like exanthemas, Jap Circ J 30 1045 1966
75 Miller G A H Thomas, M L and Medd W E Aortic arch syndrome and polymyositis with L E cells in peripheral blood Br Med J 1 7 1 1967
76 Roth L M and Kissane J M Panaortitis and aortic valvulitis in progressive systemic sclerosis (scleroderma) Am J Clin Pathol 41 287 1964
77 Ito I Aortitis syndrome with reference to detection of antiaorta antibody from patients sera Jap Circ J 30 75 1966
78 Ueda H Ito I and Saito Y Auto-antibody in the cardiovascular disease Jap J Clin Med 22 1971 1964
79 Pokoruny J and Ježková Z Significance of immunological studies in peripheral obliterating vascular disease Circ Res 11 961 1962
80 Fabius A J M Failure to demonstrate precipitating antibodies against vessel extracts in patients with vascular disorders Vox Sang 4 247 1959
81 Piomelli, S Stefanini M and Mele R H Antigenicity of human vascular endothelium Lack of relationship to the pathogenesis of vasculitis J Lab Clin Med 54 241 1959
82 Willoughby W F Pulmonary arteritis induced by cationic proteins Am Rev Resp Dis 105 50 1972

chronicity with gradual deterioration The most frequent variety of TA (65 per cent of the patients) was Type III, in which the supra aortic trunks and the abdominal aorta were involved The predominant clinical features were reduction of amplitude of peripheral arterial pulses (96 per cent), vascular bruits (94 per cent), and raised blood pressure (72 per cent), mainly resulting from renal arterial involvement (62 per cent) Heart failure (28 per cent) is rarely the result of direct coronary arteritis TA is most often confused with aortic coarctation, but usually the aortogram distinguishes these

The etiology of TA is discussed The high incidence of previous and present active tuberculous (48 per cent) in the present series and previous experimental work suggest that tuberculosis may play an important role in the etiology of TA Treatment for antihypertension and heart failure should be employed when indicated Treatment with corticosteroids requires further evaluation Treatment for tuberculosis is not justified in all cases until the exact role of tuberculosis is well established

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REFERENCES

1 Shimizu K and Sano K Pulseless disease Clin Surg (Tokyo) 3 377 1948 (in Japanese)
2 Shimizu K and Sano K Pulseless disease J Neuropathol Clin Neurol 1 37 1951
3 Ross R S and McKusick V A Diminished or absent pulses in arteries arising from the arch of the aorta Aortic arch syndrome Arch Intern Med 92 701 1953
4 Strachnan R W The natural history of Takayasu s arteriopathy Q J Med 33 57 1964
5 Martorell F and Fabré J El sindrome de obliteración de los troncos supra aórticos Med Clin (Barc) 2 26 1944
6 Savory W S Case of a young woman in whom the main arteries of both upper extremities and of the left side of the neck were throughout completely obliterated Med Chir Trans Lond 39 205 1856
7 Takayasu M Case with unusual changes of the central vessels in the retina Acta Soc Ophthalmol Jap 12 554 1908
8 Ueno A Awane Y Wakabayachi A and Shimizu K Successfully operated obliterative brachiocephalic arteritis (Takayasu) associated with the elongated coarctation Jap Heart J 8 538 1967
9 Kimoto S Surgical treatment of coarctation of the aorta with special reference to atypical coarctation Clin Surg 15 5 1960 (in Japanese)
10 Inada K Shimizu H and Yokoyama T Pulseless disease and atypical coarctation of the aorta with special reference to their genesis Surgery 52 433 1962
11 Lupi H E Sánchez T G Horwitz S and Gutierrez F E Pulmonary artery involvement in Takayasu s arteritis Chest 67 69 1975
12 Nasu T Pathology of pulseless disease Systematic study and critical review of twenty one autopsy cases reported in Japan Angiology 14 225 1962
13 Frøvig A G and Løken A C Syndrome of obliteration of the arterial branches of the aortic arch due to arteritis, Acta Psychiatr Neurol Scand 26 313 1951
14 Caccamise W C and Okuda K Takayasu s or pulseless disease An unusual syndrome with ocular manifestations Am J Ophthalmol 37 784 1954
15 Oota K Ein seltener Fall von veiderseitigem carotis-Subclaviaerchluss (ein Beitrag zur Pathologie du anastoMosis peripapillaires des Anges mit fehlendem Radialpuls) Trans Soc Pathol Jap 30 680 1940
16 Schire V and Asherson R A Arteritis of the aorta and its major branches Q J Med 33 439 1964
17 Marquis Y Richardson J B Ritchie A C and Wigle D Idiopathic medial aortopathy and arteriopathy Am J Med 44 939 1968
18 Nakao K Ikeda M Kimato S Nhtani H Miyahara M Ishimi Z Hashiba K Takeda Y Ozawa T Matsushita S and Kuromochi M Takayasu s arteritis Clinical report of eighty four cases and immunological studies of seven cases Circulation 35 1141 1967
19 Vinyuchaikul K Primary arteritis of the aorta and its main branches (Takayasu s arteriopathy) Am J Med 43 15 1967
20 Isaacson C An idiopathic aortitis in young Africans, J Pathol Bacteriol 81 69 1961
21 Correa P and Araujo J Arteritis of the aorta in young women Am J Clin Pathol 29 560 1958
22 Danaraj T J and Wong H O Primary arteritis of abdominal aorta in children causing bilateral stenosis of renal arteries and hypertension Circulation 20 856 1959
23 Steeger A and Vargas L Enfermedad de Takayasu Rev Chil Pediatr 31 377 1960
24 Sen P K Kinare S G Kulkarni T P and Parulkar G B Stenosing aortitis of unknown etiology Surgery 51 317 1962
25 Sen P K Kinare S G Engineer S D and Parulkar G B Middle aortic syndrome Br Heart J 25 610 1963
26 Paton B C Charttkanij K Buri P T and Jumbala B Obliterative aortic disease in children in the tropics Circulation 31 (Suppl) 197 1965
27 Saveleva L A and Sivkovas J Pulseless disease in childhood Pediatriia 42 67 1963 (in Russian)
28 Thurlbeck W M and Currens J H Aortic arch syndrome (pulseless disease) Report of ten cases with three autopsies Circulation 19 499 1959
29 Esclavissat M Ginefra P and Espino Vela J Enfermedad sin pulso A proposito de dos casos en mujeres jovenes Arch Inst Cardiol Mex 27 645 1957
30 Santos Botello O E Enfermedad sin pulso o sindrome de obstrucción de los troncos arteriales que nacen del cayado aórtico Rev Hosp Univ Monterrey 3 83 1956
31 Lobato O Enfermidade de Takayashu A proposito de um caso Arq Bras Cardiol 9 277 1956
32 Cesarman E Cárdenas M Escudero J Zajarías S and Contreras R Arteritis de Takayasu Observaciones clinicas y anatomopatologicas Arch Inst Cardiol Mex 33 690 1963
33 Zajarías S Rotberg T Stevens H and Durán P Arteriopatía tipo Takyasu con localizacion renovascular Arch Inst Cardiol Mex 39 499 1969
34 Rivera de Reyes A Ma Pérez Treviño C and Pérez

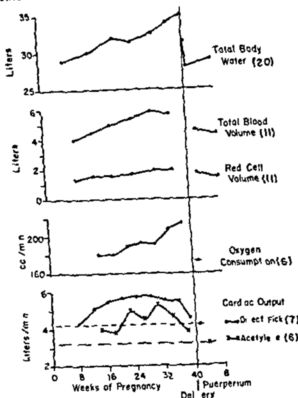


Fig 1 Hemodynamic changes during normal pregnancy and following delivery (The curves were obtained from the sources denoted by the reference numbers in parentheses)

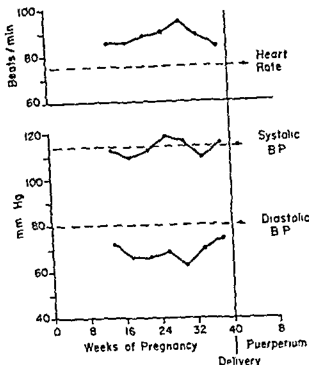


Fig 2 Changes in heart rate and blood pressure during normal pregnancy and following delivery (From Burwell C S Strayhorn W D Flickinger D Corlette M B Bowerman E P and Kennedy J A Arch. Intern Med 6? 979 1938)

nancy and because of pregnancy the sick heart must work harder than usual. For example when a pacemaker is employed during pregnancy or is already in place the heart rate is fixed at about 70 beats per minute Whereas the normal heart increases in rate as pregnancy progresses the pacemaker driven heart has a fixed rate throughout pregnancy Therefore there is no doubt that an important difference exists The cardiologist and obstetrician must make sure therefore that the heart is not overburdened or that an unnecessary demand for an extra amount of blood flow is not placed on the heart during pregnancy The extra demand due to pregnancy itself is already enough or too much Thus strenuous physical exertion and psychic stress infections with fever and other factors which increase heart work must be avoided In the presence of congestive heart failure interruption of pregnancy and certainly the avoidance of pregnancy should receive serious consideration In fact in patients with congestive heart failure and especially if a pacemaker is in use or indicated pregnancy should be avoided or interrupted early

It must be indicated at the outset of this presentation that all patients and their problems must be carefully and meticulously individualized Generalizations can only lead to serious difficulties For example when digitalizing patients[10] considerations must be made for the increase in heart rate expected for that particular stage of pregnancy

Heart rate increases during pregnancy[2] being about 10 beats per minute faster at term (Fig 2) It may increase about 20 per cent in single pregnancies and 40 per cent in twin pregnancies at term This fact alone is important not only physiologically or hemodynamically but also clinically

Blood volume may increase about 40 per cent during normal pregnancy most of this increase being plasma (Fig 1) Hemoglobin concentration

Heart disease and pregnancy

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A pregnant woman can develop any disease which a nonpregnant woman may develop In addition pregnancy may produce diseases or modifications of diseases which are peculiar to pregnancy, itself It must always be remembered that pregnancy is a dynamic state, it is changing constantly, even during the puerperium At the time of delivery and shortly thereafter the changes are extremely rapid and even dramatic These physiologic and physicochemical changes are extremely complex and little understood in spite of all that has been written about them Yet the cardiologist must be well aware of at least the relatively gross changes associated with pregnancy in order to understand cardiac diseases and cardiovascular manifestations during pregnancy and shortly after delivery It is impossible to overemphasize the need for close cooperation between the obstetrician and cardiologist at all times in order to manage properly heart disease during pregnancy At the time of delivery, and especially just before it the anesthesiologist must be informed and consulted about the cardiac problems which confront the patient and her physicians

The time to consider heart disease and pregnancy is prior to pregnancy, i e it should be decided if pregnancy should be permitted or not Should the patient have heart disease prior to pregnancy and pregnancy occur the cardiologist must follow the patient closely with the obstetrician to make decisions and introduce therapeutic measures before serious consequences can develop and especially in an effort to prevent them from developing The heart and the entire cardiovascular and renal systems should be carefully observed throughout pregnancy and after delivery because these systems can become diseased as a result of pregnancy even when the heart is normal at the onset of pregnancy The stress on the heart and circulation due to pregnancy is most important and must be clearly understood in order to appreciate the extent and nature of the changes which increase the work of the heart and affect the circulation [1-3] These changes not only reflect the reasons for the stress on the heart but may worsen heart disease already present or may precipitate heart disease

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Cardiac and circulatory changes with normal pregnancy

The important changes that develop during normal pregnancy[4,5] which should be kept in mind constantly when considering the heart and circulation during pregnancy are briefly discussed

Cardiac output is increased [6-9] during pregnancy (Fig 1) The magnitude of the increase is only known approximately After all, the methods used to measure cardiac output in intact patients are crude By the twentieth to twenty fourth week of pregnancy cardiac output is increased about 8 per cent By the seventh to eighth month of pregnancy it is increased about 14 per cent and by term it is increased about 30 per cent The increase in cardiac output is due to an increase in both cardiac rate and stroke volume Thirty to 50 per cent of the increase in cardiac output seems to be due to an increase in stroke volume and the remainder to the increase in heart rate

The cardiologist must consider this normal cardiac response to pregnancy when treating patients with heart disease Thus during preg

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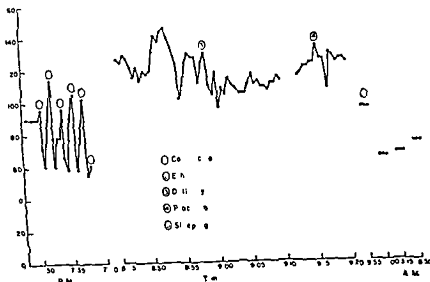


Fig 4 Time course of heart rate in a patient during labor delivery and immediately after delivery (From Burwell, C S and Metcalfe J Heart disease and pregnancy Physiology and management, Boston 1958 Little Brown & Company)

heart will be increased in accordance with the increase in venous pressure Because of the nature of the arrangement of the valves of the right ventricle right ventricular end diastolic pressure will be increased when systemic venous pressure is increased This increase in right ventricular pressure does not extend into the left side of the heart because of the intervening pulmonary circulation Furthermore this increase is merely a syndrome of circulatory changes of normal pregnancy Therefore an elevated right ventricular end diastolic pressure does not by any means indicate right ventricular congestive heart failure in the pregnant patient Other more reliable manifestations of congestive heart failure are necessary to support such a diagnosis

Supine syncope may develop in normal pregnancy When patients lie supine during the late stages of pregnancy they may develop syncopal symptoms and signs This is due to a sudden decrease in cardiac output which follows obstruction to the inferior vena cava and a possible associated vasovagal or Gower s type of phenomenon with bradycardia pallor sweating and apprehension When the patient turns on her side these symptoms disappear suddenly Unless the physician is aware of the syndrome important errors in diagnosis and treatment can follow

Edema formation is a problem to the patient not only for cosmetic reasons and because of concern about her health but also because her physician may confuse the normal response to pregnancy with accumulation of fluid with edema due to renal or cardiac disease Edema fluid accumulates in the legs ankles and feet in most if not all patients during pregnancy[19] Total body water increases throughout pregnancy (Fig 1) Patients often gain about 3 to 4 pounds of water by the tenth week of pregnancy without edema When edema is detectable the increase in body weight may reach 5 pounds or more The average increase is 4 to 5 pounds NaCl of course is increased along with the water This may increase to 500 to 600 mEq whereas the K increase is about 170 mEq The mechanisms responsible for the accumulation of the body fluids in normal pregnancy are not well known[21] The increase in venous pressure (hydrostatic pressure) and the decrease in oncotic pressure of the plasma seem to be responsible in large part for the edema Although the edema is greatest in the dependent parts of the body due to gravitational factors it is generalized, involving the face fingers arms and other parts of the body

Labor produces rather sudden and often profound changes in the cardiovascular system[5] The changes are related in large part to apprehension and fears of the mother especially of the primigravida who had her first and often traumatic psychic experience with labor With each

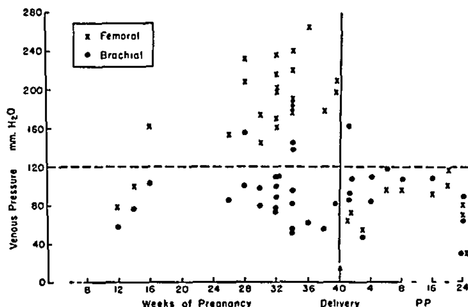


Fig 3 Changes in simultaneously recorded femoral and brachial venous pressures of women at rest in the supine position during pregnancy and following delivery The dotted line represents the upper limit of normal venous pressure (From Burwell C S and Metcalfe J Heart disease and pregnancy Physiology and management Boston 1958 Little Brown & Company)

decreases during pregnancy These changes decrease the viscosity of blood—a hemodynamic advantage Blood volume begins to increase near the sixth week of pregnancy and reaches a maximum near the fifth month after which it may begin to decrease slightly Blood volume will increase nearly 35 per cent by the twentieth to twenty fourth week of pregnancy It may even increase to 50 per cent by term Because of the inaccuracies in measurement of blood volume these volume changes are only approximations Nevertheless there is a definite increase in blood volume during pregnancy [11, 15] This must be remembered when managing normal pregnant women and, especially, pregnant women with heart disease

Circulation time, a relatively unreliable measurement quantitatively has been shown to increase as pregnancy progresses This is not surprising since cardiac output is known to increase while blood pressure changes relatively little and circulating blood volume is increased [16] The methods for determining circulation time measure linear rates of blood flow and not volume rates of flow

Arterial blood pressure changes relatively little during normal pregnancy in the absence of disease (Fig 2) There tends to be a slight decrease in systolic and diastolic blood pressure during pregnancy Peripheral arterial resistance decreases a great deal, however

The venous circulation changes with pregnancy (Fig 3) For example venous pressure in the lower extremities increases as the enlarging pregnant uterus presses upon the inferior vena cava This pressure increase is greatest when the pregnant mother rests supine[17] and the heavy uterus falls back upon the inferior vena cava Venous pressure in the lower extremities declines suddenly when the patient turns to rest on her side Venous pressure does not decline to normal nonpregnant levels however This increase in venous pressure accounts in part, for edema of the feet ankles and legs during the later stages of pregnancy All of these changes must be considered seriously when the presence of congestive heart failure is a problem or under consideration The importance of the veins in clinical medicine cannot be overemphasized [18] They are extremely active vessels and not merely passive tubes During pregnancy with the increase in blood volume and more dynamic circulation the venous system assumes a more prominent role in regulation of the total circulation of the pregnant patient For example the distended neck veins and other venous manifestations will confuse the less astute clinician Unless he is fully aware of the circulatory changes that occur during normal pregnancy, he may erroneously consider the patient to have congestive heart failure rather than expected changes of a normal pregnancy

Intracardiac pressure in the right side of the

become more and more distended with blood These vascular changes are of course normal but can be mistaken for evidence of left ventricular congestive heart failure This error in interpretation is even more likely to occur if the physician fails to realize that marginal crepitant rales are frequently present during the later stages of pregnancy These crepitant rales characteristically disappear after the patient inhales deeply a few times

General remarks

The above described changes in the cardiovascular system are important to know for all physicians who care for pregnant patients The mechanisms for their development must be understood by all physicians who are concerned with the management of pregnant patients not only to avoid making errors in diagnosis of heart disease when only normal pregnancy exists but also to be better able to recognize early and treat properly cardiac disease when it complicates pregnancy It is not possible to manage properly the many cardiologic problems related to pregnancy without this knowledge For example *the patient* often asks her obstetrician family physician or cardiologist if she is able to have a pregnancy in spite of her existing heart disease The physician therefore must know the stresses imposed by pregnancy upon the heart and circulation The physician is also often confronted with *the question* of the advisability of interrupting pregnancy because of existing cardiac disease To answer such questions properly the doctor *must know not only the stresses of the future stages of* pregnancy delivery and the puerperium but also the stresses to the mother and fetus associated with the gynecologic obstetric and anesthetic procedures associated with the interruption of the pregnancy at any particular stage

It is imperative therefore that the normal cardiovascular changes now known to be associated with normal and abnormal pregnancies be clearly understood by all physicians who are concerned with pregnant patients This is especially true of cardiologists who are consulted to assist with cardiovascular problems associated with pregnancy

Heart disease and pregnancy

The management of heart disease during pregnancy is no different from that in nonpregnant women except that consideration must be given to the extra work which pregnancy imposes on the heart The changes due to extra work load on the heart must be kept in mind constantly by both the obstetrician and the cardiologist When the cardiovascular changes associated with pregnancy are added to those due to the heart disease they tend to worsen the heart disease The diseased heart should rest not work harder Furthermore it must be remembered that obstetricians cannot cope with heart disease with or without pregnancy any better than cardiologists can cope satisfactorily with a normal or abnormal pregnancy and delivery Heart disease in pregnancy requires close cooperation between obstetrician and cardiologist at all times during the entire pregnancy and then between those physicians and the anesthesiologist and nurses at the time of hospitalization and delivery

The time to consider heart disease and pregnancy is prior to pregnancy or even when possible prior to marriage when heart disease preexists and as soon as the heart disease is detected when heart disease develops during pregnancy or during the puerperium The obstetrician should not take the responsibility of managing the patient alone once he detects or suspects cardiac disease in his patient He will fare best with his *patient* if he consults a cardiologist After all each patient is different and each patient must be individualized carefully

Acquired heart disease and pregnancy

Valvular heart disease in pregnant women should be managed medically as in any patient who is not pregnant The patient should be carefully studied clinically to make sure she is able to continue with her pregnancy This should be done early in pregnancy preferably before the third month, so that interruption of pregnancy can be achieved while it is still relatively easy obstetrically The earlier this is done the better After the third month of pregnancy the cardiologist and obstetrician should then confer to decide whether it is less hazardous to interrupt the pregnancy or to let it progress Under any circumstances the cardiologist must follow the patient carefully and manage the problems as they develop and of course make every attempt to prevent acute or chronic left or right ventricular congestive heart failure from developing

When there is a need to consider valve surgery

contraction of the uterus and associated Valsalva phenomenon (as with bowel movements), systemic venous pressure, right ventricular pressure and cardiac output increase The neck veins distend markedly and the face may become quite florid Mean arterial pressure increases and so does right and left ventricular work There is an increase in heart rate (Fig 4) Cardiac output may increase about 40 per cent, however, the accuracy of measurement of cardiac output has much to be desired Caudal anesthesia will alleviate some of these changes i e those due to pain The longer labor lasts the greater the stress upon the heart Labor is a phenomenon for young healthy people to bear It can be a tremendous burden especially when the primigravida is surrounded by the specially clothed nurses doctors, delivery room decor, instruments syringes, overhead lights anesthetic apparatus and the hissing sounds of gas flow and many other frightening things and sights It is not surprising that those patients with heart disease so often experience serious cardiac difficulties in the delivery room of modern hospitals in which the comforting influences of members of the family are absent due to the interest in sterility and prevention of infections

Furthermore heart rate and cardiac output are increased during the puerperium the latter possibly being increased 10 to 20 per cent As the postpartal period progresses heart rate and cardiac output gradually decline Stroke volume may increase, so that cardiac output may be increased later in the postpartal period in spite of bradycardia Finally body water, electrolyte retention, cardiac output heart rate stroke volume and all other alterations from pregnancy return to normal Almost immediately upon emptying of the uterus, systemic venous pressure and blood volume return to normal [2]

Stress physical and psychic will increase the changes in the cardiovascular system noted above even further Exercise and hot and humid climates and weather will increase the work of the heart of pregnant mothers Because of the influence of stress it is advisable for physicians to consider all stressful factors when managing pregnant patients with heart disease

The above changes in the cardiovascular system produced by pregnancy are often confused with heart disease *They stimulate changes due to disease of the heart* For example, basal murmurs even diastolic murmurs, may develop during normal pregnancy When murmurs of the heart are found, therefore, it is advisable to reserve commitment of significance whenever possible until delivery is over Murmurs due to pregnancy will disappear after the uterus is emptied They do not necessarily disappear immediately after delivery

Pregnancy is associated with an increase in intensity of heart sounds especially P There may be a loud third heart sound but not the cadence of a protodiastolic gallop rhythm A triple rhythm may also be produced by a loud fourth heart sound These changes in heart sound are due to the increase in cardiac output, increase in vigor of contraction of the myocardium, and increased blood volume These circulatory changes also produce a systolic mitral murmur and even a mammary souffle Furthermore patients with normal pregnancy will display dyspnea [1] and edema of the extremities which often confuse the less astute physician into erroneously rendering a diagnosis of heart disease with congestive heart failure The patients are often given digitalis and treated with other measures for congestive heart failure which they do not have The electrocardiogram will be normal The heart is not large but is horizontal in position The horizontal heart may be mistaken for an enlarged heart

The *electrocardiogram* remains normal during normal pregnancy Some electrocardiographic changes do occur however These include a shift of the electric axis of the QRS complex to the left in the frontal plane projection The increase in heart rate is recorded and the ventricular gradient reflects secondary T wave changes due to normal pregnancy but the gradient, $\hat{G}$, remains normal Occasional premature contractions or even episodes of supraventricular tachycardia may be recorded Serious cardiac arrhythmias or electrocardiographic abnormalities develop only in the presence of organic heart disease or as a result of medication

Roentgenographic examinations which should be avoided or carefully performed and used only when absolutely necessary so as to avoid injury to the fetus reveal normal size heart and normal lung fields The heart progressively assumes a more horizontal position as the uterus grows in size and the diaphragm elevates The pulmonary blood vessels become more prominent as they

and other factors than upon the pregnancy itself

Pregnant patients with these disturbances should be admitted to the hospital immediately and studied carefully The measures used in treatment should be the same as those used for nonpregnant patients Electric cardioversion and pacemakers can be used when needed with the same principles of application as in any patient

The use of *anticoagulant therapy* in pregnant patients with thromboembolic phenomena offers special difficulties The cardiologist and obstetrician must work together closely when thromboembolism becomes a problem It may even be advisable to consult a hematologist as well Heparin is the anticoagulant drug of choice since the molecule is too large to cross the placenta and affect the fetus It is better not to have to use any of the drugs at the time of delivery when it can be avoided In fact anticoagulants should be stopped at least the day of delivery and preferably a few days before

The same principle of anticoagulant therapy control as in nonpregnancy must prevail but at an ultracautious level In spite of extreme care there may be as much as a 20 per cent fetal mortality Embolectomy and femoral vein ligation should be considered and introduced when necessary However femoral vein ligation is more likely to cause large amounts of edema of the extremity in pregnant women than in nonpregnant ones

Anticoagulant therapy may be necessary for valve prostheses and if so the drug should be changed to heparin certainly a week or so prior to delivery and during the puerperal period On the day of delivery or even a few days before and after consultation with the obstetrician the drug may be stopped or the dosage markedly reduced to avoid hemorrhage with delivery The risks from thromboembolic phenomena are determined by many factors for example congestive heart failure severity of the illness stage of pregnancy atrial fibrillation and other arrhythmias heart size infection and other factors as well

The use of cesarian section in the management of patients with valvular or any type of heart disease should be determined after close discussion with the obstetrician It should be done for obstetric reasons rather than cardiac The use of oxytoxic agents should be carefully discussed by the cardiologist and obstetrician Their use is usually permissable but in low and carefully administered doses Cesarian section always carries a risk due to infection anesthesia pulmonary embolism and pneumonia Vaginal delivery with the use of forceps to hasten the second stage is preferable The anesthetic must be used carefully and must be skillfully administered with the anesthesiologist fully aware of the many problems involved with each patient Sedatives must be used carefully Ergot preparations likewise should be cautiously used if at all

Interruption of pregnancy during congestive heart failure carries a high mortality Pregnancy should be terminated early if interrupted once congestive heart failure has developed Carry the patient to term with careful and meticulous management of the congestive heart failure when pregnancy is allowed to continue or interruption of pregnancy inadvisable Remember most drugs cross the placental barrier Every effort should be made to treat the congestive heart failure vigorously in an effort to have the patient compensated by the time of delivery

The infant mortality in pregnant patients with chronic valvular disease and congestive heart failure approaches 10 per cent in favorable cases and 30 per cent in seriously ill patients When atrial fibrillation is present some centers report as high as 50 per cent fetal mortality This rate seems to be unusually high Congestive heart failure is extremely *hazardous* Therefore every effort should be made to prevent it from developing

The prognosis in pregnant patients with valvular heart disease depends on so many factors that the cardiologist is the only one who can properly weigh each of them to render a fairly accurate prognosis

Congenital heart disease and pregnancy

Pregnant mothers seldom have congenital heart disease in the U S A Most children have their congenital defects corrected in early childhood and patients with congenital defects which are not corrected or properly corrected are advised not to become pregnant Some women however do become pregnant even though they have a congenital cardiac defect At one time congenital heart disease constituted 10 per cent of all organic heart disease during pregnancy This is not so any more

Congenital heart disease during pregnancy must be individualized Since patients with congenital heart disease know of their cardiac

the cardiac surgeon should be consulted and thoroughly apprised of the problem. The simplest cardiac surgical procedure should be employed. It is best to avoid valve replacement or other procedures which require the use of cardiopulmonary bypass pump. The surgeon consulted *should be an expert and have considerable cardiac* surgical experience. There are two lives at stake. In the case of tight mitral stenosis the decision might be to do a blind commissurotomy at that particular moment and postpone more extensive surgery for another time after delivery when the obstetric state has returned to normal. Even though some pregnant patients have had successful valve surgery, even valve replacement, this surgery during pregnancy is not preferred and should be done only when absolutely necessary.

Bed rest offers the best insurance against difficulties in heart disease.[4] The patient should spend the last few weeks of pregnancy in bed and in a hospital when possible. Congestive heart failure and cardiac arrhythmias are less likely to develop during bed rest, and when they are already present, the response to therapy for congestive heart failure and arrhythmias is considerably better when the heart is resting. The measures to employ for congestive heart failure and arrhythmias are the same as for nonpregnant women with these disease states. It is beyond the scope of this presentation to describe in detail the management of valvular heart disease, congestive heart failure, arrhythmias, or any other aspect of valvular heart disease.

Acute pulmonary edema, which can occur during acute left ventricular congestive heart failure, is a severe complication of congestive heart failure. It should be prevented by proper care of the patient. It must be treated immediately and vigorously when it develops. The measures to employ are the same as for the nonpregnant patient. When it occurs late in pregnancy the prognosis is worse than in nonpregnant women and the mortality is extremely high. It accounts for about one half of the deaths in pregnant women with rheumatic heart disease. Tachycardia and infections are the most common precipitating causes of acute pulmonary edema. When one considers the changes in blood volume and hemodynamic phenomena with pregnancy, it is quite easy to understand why acute pulmonary edema can occur so quickly and tends to respond so poorly to therapy and be so fatal.

Patients with valvular heart disease alone respond well to therapy, but when myocarditis is also present the response is poor. The response depends upon the seriousness or extent of the myocardial damage. Pregnancy alone increases cardiac work 40 per cent or more. All patients with valvular heart disease with associated myocardial damage *should be treated in the* hospital. When the myocardial disease has healed, the patient may return home but should be rehospitalized and kept in bed 3 to 4 weeks prior to and 2 to 6 weeks after delivery, and her progress, the cardiac state, and therapy should be observed extremely closely.

It is well to remember that pregnant patients tend to have great difficulty with even uncomplicated mitral stenosis. They are prone to acute pulmonary edema. This is to be expected in view of the increase in blood volume, increase in cardiac output, high systemic venous pressure, and the large uterus. The mitral stenosis results in a dam in the stream, so that the reduced plasma proteins, increase in blood volume, and increase in capillary hydrostatic pressure predispose to pulmonary edema of varying extent depending upon the circumstances.[5] The hemodynamic principles and therapeutic approach are obvious to the well trained cardiologist.

It has been stated that 20 to 25 per cent of patients with mitral stenosis during pregnancy develop congestive heart failure, 7 per cent develop atrial fibrillation, about 3 per cent develop supraventricular tachycardia, and about 3 per cent develop pulmonary and/or systemic embolism. Subacute bacterial endocarditis on the damaged valve is not common.

Mitral regurgitation, of course, varies in degree. When it is severe, atrial flutter, fibrillation, embolism, and congestive heart failure become even greater problems as the left atrium and left ventricle dilate.

Aortic stenosis and *aortic insufficiency* tend to offer less difficulties than advanced mitral valve disease during pregnancy. The management of the cardiac disease should be left to the cardiologist.

Cardiac arrhythmias and *conduction disturbances* can occur in pregnant women as well as in nonpregnant ones. The presence of organic heart disease predisposes to arrhythmias in all patients and probably more so in pregnant ones. As a rule these disturbances in the heart beat are more dependent upon the type and severity of the heart disease, the drugs and therapeutic measures used

glect their care and fail to see their physicians regularly and then develop the eclamptic state or hypertensive encephalopathy with the typical syndrome at or near term This syndrome can be prevented with good medical care in which the patient follows advice and instructions for anti hypertensive therapy with home recording of blood pressure

When blood pressure tends to increase rapidly the amount of edema increases and proteinuria develops or increases When funduscopic exami nation reveals typical retinal changes of serious disease the patient should be immediately ad mitted to hospital and vigorous therapy insti tuted When the blood pressure reaches about 180/110 the development of serious difficulties should be anticipated With the present state of knowledge and the availability of effective anti hypertensive drugs and antibiotics for urinary tract infections eclampsia should be prevented Severe congestive heart failure can develop acutely and result in death Fatal or serious cardiac arrhythmias must be considered at all times Toxemic cardiomyopathy may develop and offer future and prolonged difficulties in health and care Acute pulmonary edema can occur sud denly when fluid is used in excessive amounts in the presence of impaired renal function excessive salt intake and impaired cardiac function Elec trocardiographic abnormalities are present in practically all patients with toxemia of pregnancy These are ST segment and T wave changes along with slurring and notching of the QRS complexes Some areas of the myocardium may not undergo electric activity and in turn fail to contract

Any form of renal disease can exist in pregnant patients The various types or stages of glomeru lonephritis and pyelonephritis are among the most common forms of renal disease that exist in pregnant women Urinary tract infections both acute and chronic are also commonly present during pregnancy Pregnancy tends to worsen all types of urinary tract infections renal disease and hypertensive states Because toxemia of preg nancy is so often associated with disturbances in cardiac function a cardiologist should be con sulted routinely for patients with toxemia of pregnancy Furthermore any cardiologist who is regularly concerned with heart disease and preg nancy must be fully informed about renal disease and renal function with and without hypertensive states The eclampsias of pregnancy almost routinely are associated with the many problems of renal and hypertensive disease states For example acute pulmonary edema due either to injudicious therapy or solely to acute congestive heart failure is a serious often fatal and difficult clinical state to manage at term It also can develop or worsen in puerperium

Eclampsia of pregnancy presents with many of the manifestations of acute glomerulonephritis

Obviously it is extremely important to eval uate carefully the renal state and the state of arterial blood pressure prior to pregnancy No obstetrician should feel proudly satisfied because a mother with urinary tract infection renal disease or hypertension survived pregnancy and produced a live birth unless she is in good health afterwards to rear the infant and all siblings for years It is easy to reproduce an infant—it is done in nine months—but it is extremely difficult to rear one The rearing process and the responsibil ities continue throughout the mother s life The burdens can be considerable

Miscellaneous hypertensive diseases Some of the rare forms of hypertension cannot be discussed in this presentation For example pheochromocytoma carries an extremely high maternal and infant mortality The obstetrical management of this state must include a cardiol ogist and an endocrinologist also Paroxysmal tachyarrhythmias and acute pulmonary edema account for most of the deaths from pheochromo cytoma which usually occur at term or at the time of delivery The tumor should be detected and removed prior to pregnancy This could be done if patients were educated to consult physi cians for study and clearance of their state of health prior to pregnancy just as is done prior to elective surgery

Postpartal and peripartal cardiomyopathy

A pregnant woman can have any type of cardiomyopathy that a nonpregnant one can develop but only a pregnant woman may develop a cardiomyopathy peculiar to pregnancy near term or shortly after delivery The cardiomyopa thy can present with a broad spectrum of mani festations and extent of myocardial disease The disease can be so mild and subtle as to be evident only from the electrocardiogram or so extensive as to be a state of intractable irreversible and fatal congestive heart failure These variations of

disease long before pregnancy, they usually consult their doctors for advice prior to marriage and pregnancy Patients with cyanotic defects have a bad prognosis, and those with pulmonary hypertension particularly have a bad prognosis When a congenital defect is detected during pregnancy it should be studied immediately, using cardiac catheterization only when neces sary When pulmonary hypertension is present, pregnancy should be interrupted during early pregnancy If pregnancy is already in the third trimester, the cardiologist and obstetrician should attempt to bring the pregnancy to term with vaginal delivery But, the prognosis is always poor Pregnancy should be prohibited in the presence of pulmonary hypertension and cyanotic congenital heart disease

Surgical correction of congenital heart defects should be undertaken during pregnancy only when mandatory The decision about surgical management during pregnancy should be the result of careful consideration by cardiac surgeon cardiologist, obstetrician, and anesthesiologist

Subacute bacterial endocarditis which may develop during pregnancy complicated by con genital defects or valvular heart disease, should be treated with antibiotics, and with surgical assistance only under special circumstances

It is obvious that all correctable congenital defects should be managed surgically before preg nancy Those patients with defects which carry poor prognosis should avoid pregnancy

Congenital cardiac defects which carry a prog nosis too poor to permit pregnancy are cyanotic defects, those defects with pulmonary hyperten sion, isolated tight pulmonary stenosis, Eisen menger s syndrome, Ebstein s disease, coarctation of the aorta with marked hypertension and complete heart block Some of these are correct able surgically and if corrected first then preg nancy can be permitted

All congenital heart defects are associated with at least a slight increase in risk during pregnancy The cardiologist can determine the risk progno sis, management, and future care

Hypertension and pregnancy

Patients with any type of hypertension may become pregnant Those with poor renal function or very high arterial blood pressure should avoid pregnancy Renal function should be good and pyelonephritis should not exist at the time of pregnancy The pregnant uterus, itself, predis poses to urinary tract infections or produces exacerbation of infections when they already exist A patient with hypertension should have the hypertension evaluated properly, therapy instituted, and the pressure controlled prior to pregnancy Home recording of blood pressure is extremely valuable for the control evaluation of hypertension, and regulation of drug dosage and type[26] Labile blood pressure and psychogenic factors which elevate arterial blood pressure can only be evaluated properly with home record ings

Mild essential hypertension does not influence the prognosis during pregnancy, whereas malig nant hypertension does When the latter exists pregnancy should be avoided or interrupted when possible The decision to interrupt pregnancy should be made in close consultation with the obstetrician

When hypertension is present, the pregnant mother must be watched closely with frequent careful, complete and proper types of urinalysis Renal function may be checked occasionally with PSP excretion when necessary Home recording of blood pressure is mandatory to follow the course of the disease and to regulate therapy and titrate drug dosage[26] As the terminal period of pregnancy is entered the patient should be seen frequently and advised to have her blood pressure recorded at home more frequently When the pressure is very high she should be admitted to hospital 2 to 3 weeks prior to delivery The medical management and drugs to employ are the same as for any hypertensive patient The regula tion of diet and salt intake are extremely impor tant However the control of the blood pressure should offer no unusual difficulties

At the time of delivery the obstetrician and anesthesiologist should consult with the cardiolo gist regarding the stopping of certain antihyper tensive drugs before delivery

Toxemia of pregnancy offers special problems The eclamptic state can be prevented when patients are watched closely Most instances of eclampsia develop in patients who do not see their physicians regularly or follow advice closely Some patients who are free from hypertension at the onset of pregnancy develop typical toxemia of pregnancy at the time of delivery There are also the patients with essential hypertension chronic glomerulonephritis or nephrosclerosis who ne

puerperium These must all be properly considered

Thus when the pregnant patient has a diseased heart the cardiologist must not only be a master cardiologist but should have extensive experience with bedside cardiology and cardiology in pregnant patients and be a well trained internist The choice and use of drugs and communication and understanding among doctors nurses and other attendants are extremely important In the presence of heart disease extra care at all times is necessary not only to assure good results at the time of delivery but also to prevent serious and hazardous events from developing even later in the lives of mother and baby In addition the fetus as well as the mother must receive adequate consideration and attention at all times After all the object is also to deliver a live baby

The advantages and disadvantages and dangers of drugs and other therapeutic agents remain important during the deliberations concerning the pregnant patient with heart disease Fortunately since the pregnant patient is always young the factors related to aging are never present to complicate deliberations and therapy

To manage the patient with heart disease who contemplates pregnancy or who is pregnant requires the attention of a master cardiologist He should be consulted early so that he can anticipate problems and outline measures to prevent their occurrence Furthermore when he is fully acquainted with the patient he is much better prepared to offer the best service when emergencies develop Too frequently the cardiologist is consulted when the conditions are irreversible often for both fetus and mother This can be avoided with proper planning

Finally any patient who has had cardiovascular and/or renal disturbances of any kind should not be discharged as being well at the arbitrarily set time of the sixth week postpartal examination A prolonged follow up is always necessary Many patients may present with essentially normal manifestations or subtle cardiologic disease states often overlooked during a rapid cursory postpartal examination Such patients later present with advanced and even irreversible cardiovascular and renal disease states that should have been treated all along following delivery The obstetrician who has completed his responsibilities should then refer the patient to the cardiologist for continuation of care and follow up observation and management This practice would prevent many serious consequences of cardiologic diseases of pregnancy

REFERENCES

1 Hammond J Browne B F, and Wolstenholme C E, editors Toxaemias of pregnancy Human and veterinary A Ciba Foundation Symposium Philadelphia 19.0 The Blakiston Company

2 Burwell C S and Metcalfe J Heart disease and pregnancy Physiology and management Boston 1958 Little Brown & Company

3 Szekely P, and Snaith, L Heart disease and pregnancy Edinburgh and London 1974 Churchill Livingstone

4 Pyorala T Cardiovascular response to the upright position during pregnancy Acta Obstet Gynecol Scand 45 (Suppl 5) 1966

5 Kerr M G Cardiovascular dynamics in pregnancy and labour Br Med Bull 24 19 1968

6 Burwell C S Strayhorn W D, Flickinger D, Corlette M B Bowerman E P and Kennedy J A Circulation during pregnancy Arch Intern Med 62 979 1938

7 Hamilton H F H The cardiac output in normal pregnancy As determined by the Cournand right heart catheterization technique J Obstet Gynecol Br Emp 56 548 1949

8 Bader R A, Bader M E, Rose D J and Braunwald E Hemodynamics at rest and during exercise in normal pregnancy as studied by cardiac catheterization J Clin Invest 34 1524 1955

9 Rovinsky J J, and Jaffin H Cardiovascular hemodynamics in pregnancy III Cardiac rate stroke volume total peripheral resistance and central blood volume in multiple pregnancy Synthesis of results Am J Obstet Gynecol 95 87 1966

10 Burch, G E Elegant digitalization for congestive heart failure AM HEART J 83 543 1972

11 Caton W L Roby C C Reid D E Caswell R Maletskos C J Fluharty R G and Gibson J G, II The circulating red cell volume and body hematocrit in normal pregnancy and the puerperium By direct measurement using radioactive red cells Am J Obstet Gynecol 61 1207 1951

12 Rovinsky J J and Jaffin H Cardiovascular hemodynamics in pregnancy I Blood and plasma volumes in multiple pregnancy Am J Obstet Gynecol 93 1 1965

13 Rovinsky J J Blood volume and the hemodynamics of pregnancy in Philipp E E Barnes J and Newton M editors Scientific foundations of obstetrics and gynaecology Philadelphia 1970 F A Davis Company pp 332 340

14 Lund C J and Donovan J C Blood volume during pregnancy Significance of plasma and red cell volumes Am J Obstet Gynecol 98 393 1967

15 Adams, J Q Cardiovascular physiology in normal pregnancy Studies with the dye dilution technique Am J Obstet Gynecol 67 741 1954

16 Burwell C S Circulatory adjustments to pregnancy Bull Johns Hopkins Hosp 95 115 1954

17 Lees, M M Scott D B Kerr M G and Taylor S H The circulatory effects of recumbent postural change in late pregnancy Clin Sci 32 453 1967

18 Burch G E A primer of venous pressure Springfield Ill 1972, Charles C Thomas Publisher

19 Robertson E G The natural history of oedema during pregnancy J Obstet Gynecol Br Commonw 78 520 1971

course, are found in all forms of cardiomyopathy

Patients with *acute myocarditis* should be placed in bed immediately and treated accordingly The extra work of pregnancy alone placed upon a seriously diseased myocardium already overburdens the heart Any extra work associated merely with ambulation is detrimental There is no evidence that pregnancy predisposes the heart to myocarditis due to viral or bacterial infections, but it might Acute myocarditis is a serious illness at any time and especially during pregnancy It may result in sudden death especially during labor or during the puerperium In the presence of valvular heart disease it can precipitate congestive heart failure The management of acute myocarditis is the same as for cardiomyopathy, which has been discussed elsewhere previously [22] Patients with acute myocarditis sustain stress of any sort poorly

Postpartal cardiomyopathy has been reserved to indicate a cardiomyopathy that develops only postpartally between the second and twentieth weeks after pregnancy [7, 8] The patient will have had no evidence of any sort of cardiac disease prior to that time certainly none during pregnancy The delivery and puerperium are initially normal in every respect and so is the heart Then by the second to sixth week or even up to the twentieth week the patient begins to complain of dyspnea on exertion, palpitation, and edema of the feet and ankles A study of the patient reveals the manifestations of myocardial disease The damage and cardiac enlargement vary of course from mild to extensive Postpartal cardiomyopathy is found most frequently in Negroes but occurs among other races as well White women of the U S A rarely develop this cardiomyopathy whereas black women of the U S A do The disease is fairly common in Central and South America It responds rapidly to absolute bed rest and therapy for congestive heart failure provided therapy is started early and during the incipiency of the disease When the disease is neglected and treated late, the response is less satisfactory, or even poor and the disease state is often irreversible

Peripartal cardiomyopathy refers to the cardiomyopathy which occurs just prior to during or immediately after delivery The manifestations and management are the same as for postpartal cardiomyopathy

The etiology or mechanism by which these myocardial diseases occur are unknown The etiology has been postulated to be endocrine viral bacterial metabolic immunologic, or autoimmunologic, or related to other factors too numerous to list There is really no generally accepted etiologic concept as yet Nevertheless, the syndromes exist They are highly fatal and require constant consideration by the obstetrician and cardiologist Prompt, vigorous therapy must be introduced immediately and relentlessly as described in detail elsewhere [28]

Miscellaneous cardiac disease states such as idiopathic subaortic hypertrophic stenosis pericarditis, relatively uncommon congenital defects subacute bacterial endocarditis, and others have not been discussed in these brief considerations Nevertheless, they are extremely important and require management jointly by cardiologist and obstetrician Likewise the problems of drugs drug reactions, drug incompatibility, and other aspects of therapy have not been included in these discussions but do require close attention The cardiologic problems are extensive and extremely variable

General remarks

Heart disease in pregnancy involves all the possible problems of cardiology except they occur in a pregnant woman Therefore the above discussions could only be brief There are however certain changes associated with normal pregnancy that involve the entire circulatory system including the heart which the obstetrician and cardiologist must keep in mind at all times All these normal physiologic changes impose an extra load on the heart They become progressively greater as pregnancy progresses and reach their peak at the time of delivery At the time of delivery the influence of drugs the environment anesthesia psychic stress and concern over the outcome, family problems at home and many other factors affect the general medical and cardiologic state of the patient These factors must all be properly evaluated and their respective importance adequately considered It is evident, therefore that the experience and clinical ability of the attending physicians cannot be overemphasized Furthermore it must be remembered that the kidneys lungs urinary system, and all organs of the body also enter into the complex problems of pregnancy delivery and

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Present state of alpha and beta adrenergic drugs III Beta blocking agents

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Propranolol is the only beta adrenergic receptor blocking agent approved for use in the United States The only uses for which it is currently approved by the FDA are tachyarrhythmias obstructive cardiomyopathies angina pectoris and hypertension In the United Kingdom and throughout the rest of the world there are at least seven other beta blockers available for clinical use And in addition to the FDA approved indications these are used to treat *migraine* essential tremor anxiety schizophrenia and myocardial infarction

The clinical studies of Prichard first with pronethalol and later with propranolol in angina pectoris served to introduce propranolol into clinical medicine in 1965 The general premise for the use of beta blockade in angina was to reduce the exercise induced work of the heart If the work is not allowed to increase then exercise tolerance should be improved At the same time the intake of nitroglycerin would be decreased There is no question that propranolol and all of the other beta blocking agents are effective in the treatment of angina There is still a question of how exactly they do work

There have been several published studies that show propranolol to be ineffective in angina In most of these it is apparent that the dosage used was too small The pharmacokinetics of propranolol in humans is unique With oral administration the liver avidly clears propranolol so that very little gets into the general circulation This clearance varies twentyfold between patients so that the relationship between oral dosage and plasma concentration is extremely variable To achieve an effective plasma level the daily oral dose can vary from 10 to 800 mg or more On the other hand the response to an intravenous dose is relatively constant between patients

The effectiveness of propranolol in angina is demonstrated by the need for caution in suddenly withdrawing the drug A patient whose exercise tolerance has been markedly increased by the drug could suddenly become vulnerable to acute angina or even infarction

Propranolol is not a coronary vasodilator In fact it may even reduce total coronary flow In Prinzmetal s variant angina beta blockade allows the endogenous catecholamines to cause measurable coronary vasoconstriction The constriction is the result of unopposed alpha receptor action

Propranolol is indicated in any type of fast *arrhythmia* Sinus tachycardia is readily controlled by propranolol In fact sinus bradycardia always occurs when propranolol is given This effect may be obscured by some forms of ectopic arrhythmia but all patients with a normal rhythm will show bradycardia Propranolol by slowing atrioventricular conduction is effective in atrial fibrillation or flutter Digitalis however continues to be the drug of first choice

The effect of propranolol on ventricular fast arrhythmias is more variable If caused by catecholamines or digitalis these arrhythmias respond well to beta blockade These tachycardias include those of hyperthyroidism pheochromocytoma, or some forms of anesthesia

Propranolol is useful for treating hypertrophic subaortic stenosis In this condition the positive inotropic action of isoproterenol (beta agonist) increases the outflow pressure gradient resulting in angina or syncope Propranolol blocks this action of isoproterenol In many cases propranolol prevents a similar response to exercise

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20 Haley H B and Woodbury J W Body composition and body water metabolism in normal pregnancy Surg Gynecol Obstet **103** 227 1956
21 Hytten F E and Thomson A M Water and electro lytes in pregnancy Br Med Bull **24** 15 1968
22 Brown E Sampson J J Wheeler E O Gundelfinger B F and Giansiracusa J E Physiologic changes in the circulation during and after obstetric labor AM HEART J **34** 311 1947
23 Novy M J and Edwards M J Respiratory problems in pregnancy J Obstet Gynecol **99** 1024 1967
24 Burch G E and Giles T D Diagnosis and treatment of cardiomyopathy *in* Changing concepts in cardiovascular disease the Proceedings of the American College of Cardiology Baltimore 1972 The Williams & Wilkins Co pp 80-95
25 Ueland K Novy M J and Metcalfe J Hemodynamic responses of patients with heart disease to pregnancy and exercise Am J Obstet Gynecol **113** 47 1972
26 Burch G E and DePasquale N P The value of home recordings of blood pressure in the management of patients with arterial hypertension Am J Med Sci **240** 273 1960
27 Walsh J J and Burch G E Postpartal heart disease Arch Intern Med **108** 817 1961
28 Burch G E McDonald C D and Walsh J J The effect of prolonged bed rest on postpartal cardiomyopathy AM HEART J **81** 186 1971

here is evidence that a decrease in central sympathetic outflow is produced This effect has een suggested as a mechanism of antihyperten sive action

As far as can be determined all of the beta blockers are clinically equivalent They may differ as to dosage schedules but all are effective in angina hypertension migraine arrhythmia etc As can be seen in Table I the only pharma codynamic action common to all of them is beta receptor blockade It follows from this that beta blockade is the only clinically important effect The antihypertensive action then is due primar ily if not exclusively to beta blockade A decrease in cardiac output and a negative inotropic effect are the result of chronic beta block The latter effect could reset the barostat of the carotid sinus to a lower level of control

Adverse effects

Most of the adverse effects of propranolol are due to beta blockade An increase in airway resistance in asthmatics is the principle non cardiovascular adverse effect Even the cardio selective agents will do this however higher doses would be needed

For any cardiovascular use the first dose of a beta blocker is the most dangerous This dose will induce an unknown amount of beta blockade in an unknown environment of adrenergic activity It could be enough to remove all positive drive to the heart resulting in acute failure Therefore the first dose should be small Once the patient has been started on a regimen of propranolol increases in dosage by as much as 25 per cent are not dangerous

Bradycardia can be considered an adverse effect However a heart rate of 50 beats per minute or less should not be a reason to stop the drug unless there is evidence that the slow rate has an ill effect on the circulation

Propranolol does increase peripheral resistance slightly and has a tendency to produce hypogly cemia The former effect may worsen disorders with impaired circulation the latter effect may exaggerate dietary hypoglycemia

In common with other new drugs the beta blocking agents occasionally show adverse effects apparently unrelated to their basic pharmacody namic effect For propranolol these are central nervous system depression nausea vomiting

Table I Clinically useful beta blockers

Name	ISA†	MSA‡	PRA§
Propranolol	0	+	+
Sotalol	0	0	?
Alprenolol	+	+	+
Oxprenolol	+	+	?
Pindolol	+?	0	?
Timolol	0	0	+
Practolol	+	0	?
Atenolol	0	0	0

*Cardioselective
†Intrinsic sympathomimetic activity
‡Membrane stabilizing activity
§Decrease in plasma renin activity

blood dyscrasias and reversible alopecia Prac tolol has a unique adverse effect In a few patients after months of treatment an oculo cutaneous syndrome appears This includes ocular changes otitis media and sclerosing peritonitis No other beta blocker has as yet shown this effect

Summary

The beta blocking agents are valuable drugs in cardiology They are effective in any fast arrhyth mia Together with nitroglycerin beta blockers are drugs of first choice in angina As antihyper tensives they have advantages that should make them drugs of first choice For migraine the beta blockers are equal to any other type of drug With more study their place in treating anxiety will be clarified And without question other uses will be found

It is difficult for this author to understand the attitude of the FDA to this class of drugs To limit the American physician to only one drug in this large group of drugs is unheard of Although it can be argued that propranolol is the best one there are obvious cases where another drug would be better For example propranolol induces nightmares in a few patients There is evidence to show that timolol does this less frequently

FDA delay in approval of propranolol for essen tial hypertension is totally incomprehensible Other approved drugs are less effective and much more toxic Propranolol and the other beta blockers are safe and effective The adverse beta effects are easily controlled or avoided The other adverse effects are no more frequent than with any other class of drugs and all are reversible It is to be hoped that science and common sense will prevail over bureaucratic indecision

Other uses of propranolol

Propranolol is an effective safe antihyperten sive agent[4] Administered in adequate dosage in conjunction with a thiazide diuretic propranolol will lower diastolic pressure in the majority of patients with essential hypertension Propranolol has significant advantages over other antihyper tensives it does not produce postural or exercise induced hypotension and it lowers pressure in the supine position To date no evidence has been found to show that propranolol will adversely affect life style

Beta blockade has been used to treat myocar dial infarction In addition to controlling arrhythmias propranolol is said to improve oxygenation of the myocardium The mechanism is presumed to be a decrease in oxygen require ment by reducing heart rate and myocardial contractility There is also evidence that beta blockade is a useful prophylactic agent to prevent a second myocardial infarction Great care must be taken in using propranolol in acute infarction to prevent excessive cardiac depression

Propranolol has been shown to be effective in anxiety A proposed mechanism is the reduction of the peripheral hyperdynamic circulatory response to anxiety Removal of this peripheral effect seems to interfere with a positive feedback mechanism Acute and chronic alcoholism seem to be benefited by this same action

The ability of propranolol to control migraine was a serendipitous discovery Patients being treated for angina or hypertension with propra nolol noted that their migraine had vanished Subsequent studies showed that propranolol was effective in many cases of migraine The mecha nism of action is completely unknown

Another interesting effect of propranolol is the control of essential tremor This is a peripheral action at the neuromuscular junction The so called beta 2 agonists among which is terbutal ine cause tremor as a side action in some patients This can be prevented by propranolol The tremor of parkinsonism is not affected by beta blockade

Other beta blockers[3]

In the United Kingdom, and elsewhere there are at least seven beta blockers in clinical use A few others are still being tested A brief consider ation of these will serve to illustrate the basic mechanism of action that makes the beta blockers clinically useful

Some of the beta blockers are partial agonists They are said to have intrinsic sympathomimetic action (ISA) The first dose will produce some beta effects such as tachycardia and hypotension There is no evidence that this effect has clinical significance ISA does not prevent the drug from increasing airway resistance in asthmatic pa tients And it does not counteract the cardiac failure resulting from high doses of beta blockade And as has been shown in animals the ISA becomes blocked by the drug itself after a few doses

Some of the beta blockers including proprano lol have a local anesthetic action This is called the membrane stabilizing action (MSA) or the quinidine like action or the nonspecific myocar dial depressant effect Although this may appear to be significant in treating arrhythmias it is clinically irrelevant The concentration required to show this action is 50 to 100 times greater than any concentration achieved clinically

Some of the beta blockers are cardioselective At first it was thought that these drugs were cardio specific and that there were two kinds of beta receptors An examination of a large variety of beta agonists and blocking agents shows a different explanation Each receptor–effector pair has a unique dose response ratio for each agonist and blocking agent With isoproterenol and propranolol all of the dose response ratios are about the same these two agents act equally on all beta receptors Practolol and atenolol show at least two different ratios the cardiac receptors are blocked by small doses the bronchial smooth muscle receptors are blocked with large doses The importance of this view is that under clinical use the doses used may be so large that cardiose lectivity may not be apparent

Some beta blockers including propranolol will lower plasma renin activity (PRA) The effect has been postulated as the mechanism of the antihypertensive action The plasma renin activi ty must be related to sodium excretion to provide a proper index of activity Some of the beta blockers have no significant effect on PRA However this activity has not as yet been deter mined for every beta blocker

Some of the beta blockers including proprano lol enter the central nervous system For these

Prelymphatic lymphatic drainage of the brain

Only vessels lined by endothelial cells are called lymphatics and only fluid inside their lumina is designated as lymph. Due to the fact that the composition of tissue fluid and that of lymph is not necessarily identical—in fact it very often differs very much—a clear distinction must be made between these two fluids too. Connective tissue channels through which, on the surface of fibers, films of tissue fluid containing plasma proteins stream from blood capillaries to initial lymphatics are called "prelymphatics." I have proposed that one should distinguish between short prelymphatics (e.g., in the mesenterium, where initial lymphatics and blood capillaries are lying closely together), long prelymphatics (e.g., in the liver, where they cover the distance between Disse's spaces and the periportal spaces of Mall), and very long prelymphatics. Very long prelymphatics are situated in the adventitia of blood vessels in regions lacking lymphatics but needing a lymphatic drainage. Examples for this are the hamster cheek pouch and the brain. In all other regions additional *vasa lymphatica vasorum* are directly draining the walls of the larger blood vessels.

The continuous escape of plasma proteins from blood capillaries into the tissues and the vital role lymphatics play in their reabsorption are well-established facts; a failure of this function will result in high protein edema and moreover in cellular lesion, eventually necroses. As a consequence various lymphostatic diseases will arise. Permeability of blood capillaries varies from organ to organ. Liver sinusoids are generally regarded as those with the highest, blood capillaries of the dermal tissues as those with the lowest permeability. Due to the dogma of a BBB which completely hinders plasma proteins from entering the brain, cerebral blood capillaries are rarely mentioned in this scale. The fact that there are no lymphatics in the brain fits perfectly into this dogma. It has seemed to be confirmed further by a biological proof of great interest. Tissues transplanted between individuals of dissimilar genetic background do not survive, but it is considered that the brain is privileged in this regard. This privilege is explained by the absence of a lymphatic drainage, i.e., of the afferent arc leading to the regional lymph nodes where immunologic rejection should be triggered.

As most dogmas, these two are false as well. Labelled plasma albumin after intravenous injection has been shown to enter those areas of the brain which entirely lack a BBB (e.g., area postrema, pineal body) and to accumulate there as much as in the liver. Moreover, from here the protein molecules penetrate deeply through the intercellular spaces into regions possessing a BBB. The same holds true for protein markers injected into the cerebrospinal fluid (CSF); they can be followed deeply into the neuropil. Furthermore, it is well known that throughout the body plasma proteins enter the walls of the blood vessels through their endothelial linings, being reabsorbed by vasa lymphatica vasorum ("plasmatic perfusion"). There is no reason to assume that major cerebral blood vessels are not perfused by blood plasma. Various inflammatory processes and hemorrhages leading to an inflow of protein into the brain substance may completely heal. About 100 mg of plasma protein are entering CSF per day in the healthy human; in acute encephalitis or meningitis, however, as much as 500 mg or more protein may be present in the CSF with a considerably increased turnover.

The dogma of an absolute BBB for plasma proteins must be abandoned. Furthermore, Lance has shown that the brain possesses no distinct privilege with regard to allogenic tissue.

Three possibilities arise—each for itself or in various combinations—to explain protein clearance from the intracranial site:

1. In spite of the absence of lymphatics from the brain tissue proper, a lymphatic drainage does exist.
2. Proteins are leaving the intracranial site through the blood vessels.
3. Proteins are disposed of by cellular uptake and degradation.

For a century the existence of such connections has been well established. Various tracers after intrathecal injection rapidly appear in cervical lymph nodes. These tracers have been described to travel along the leptomeningeal sheaths of cranial and spinal nerves, to accumulate in their cul-de-sacs, and to pass into the epidural loose connective tissue, middle ear, and nasal mucosa, and are picked up by the initial lymphatics situated here. This pathway has been called "perineuro lymphatic" by Bowsher.

Electron microscopy has led to a proper identification of the various spaces described in the central nervous system. Most of them turned out to be artefacts; what remained as a reality is the *adventitial* (or perivasal) space of Virchow and Robin. This space extends from the depths of the *capillary* bed along the course of the blood vessels through the arachnoid space into the general tissue space of the body.

Cserr injected into the rat brain Blue dextran 2000. The pattern of distribution of the tracer indicated a bulk flow in association of blood vessels; according to the author these results indicated "The need for reexamination of the old questions

1. of continuity between cerebral interstitial fluid (ISF) and the fluid in the perivascular spaces and
2. of a possible (?) lymphatic" drainage of ISF into CSF via perivascular spaces."

The possibility of such a roundabout lymphatic pathway through the perineuro lymphatic connections certainly exists. But there exists a direct one as well, which has been designated as "hemangiolymphatic" by me.

"The brain has no true lymphatics, and is dependent on the perivascular system for the removal of effete and superfluous

Lymphatic drainage and cellular protein mastering ha[s] already been sh[ow]n [to] act in extracranial tissues in a syn[e]rgestic m[a]nner.

REFERENCES

1 Prichard B N C Beta adrenergic receptor blocking drugs in angina pectoris Drugs 7 55 1974
2 Shand D G Pharmacokinetic properties of beta adrenergic receptor blocking drugs Drugs 7 39 1974
3 Furberg C D Beta adrenergic blocking drugs in hyper trophic obstructive cardiomyopathies certain functional heart disorders and Fallot s tetrology Drugs 7 106 1974
4 Simpson F O Beta adrenergic receptor blocking drugs in hypertension Drugs 7 85 1974
5 Ahlquist R P Adrenergic beta receptor blocking agents Progr Drug Res 20 (in press 1976)
6 Buhler F R Laragh J H Baer L et al Propranolol inhibition of renin secretion N Engl J Med 287 1[illegible] 1972
7 Beumer H M Adverse effects of beta adrenergic receptor blocking drugs on respiratory function Drugs 7 130 1974

REFERENCES

1 Foldi M Physiologie und Pathophysiologie des Lymphgefasssystems in Meesen H ed Handbuch der allgemeinen Pathologie Vol 3 part 6 Berlin Heidelberg New York 1972 Springer Verlag
2 Casley Smith J R The lymphatic system in inflammation, in Zweifach B W Grant L and McCluskey R T, editors The inflammatory process New York/London 1973 Academic Press Inc p 161
3 Foldi, M Diseases of lymphatics and lymph circulation Springfield 1969 Charles C Thomas Publisher
4 Foldi M Kluken N and Collard M Praxis der lymphgefass und Venenerkrankungen Stuttgart 1974 Gustav Fischer Verlag
5 Foldi M Physiologie des lymphgefasssystems Angiologica 8 212 1971
6 Witte S Goldenberg D M and Schricker K T Die Ausbreitung von Fluorescenzfarbstoffen in der Hamsterbackentasche Z Exp Med 148 77 1968
7 Foldi, M Lymphostatische Krankheitsbilder Herz Kreislauff 2 217 1970
8 Brown P Albumin connective tissue and the blood brain barrier Bull Johns Hopkins Hosp 108 200 1961
9 Wagner H J Pilgrim C and Brandl J Penetration and removal of horseradish peroxidase injected into the cerebral fluid Role of cerebral perivascular spaces endothelium and microglia Acta Neurophathol (Berl) 27 299 1974
10 Yoffey J M and Courtice F C Lymphatics lymph and the lymphomyeloid complex London/New York 1970 Academic Press Inc
11 Lance E M A functional and morphologic study of intracranial thyroid allografts in the dog Surg Gynecol Obstet 125 529 1967
12 Lance E M A functional and morphological study of intracranial parathyroid allografts in the dog Trans plantation 5 1471 1967
13 Casley Smith J R The actions of the benzo pyrones on the blood tissue lymph system Folia Angiologica 19 6 24 1976
14 Foldi M and Foldi Borcsok E Lympho tase und Vitamine Angiologica 10 101 1973
15 Foldi Borcsok E and Foldi M Lymphedema and vitamins Am J Clin Nutr 26 185 1973
16 Key A and Retzius G Studien in der Anatomie des Nervensystems und des Bindgewebes Stockholm 1876 P A Norstedt & Soner
17 Iwanow G Uber die Abflusswege aus den Subarachnoidal raumen des Gehirns und Ruckenmarks und uber die Methodik ihrer intravitalen Untersuchung Z Exp Med 64 356 1928
18 Field E J and Brierley J B The retro-orbital tissue as a site of outflow of cerebrospinal fluid Proc R Soc Med 42 447 1949
19 Arnold W Nitze H R and Ritter R Anatomical relations between the cerebrospinal fluid (CSF) and the lymphatic system in the region of the head and neck Arch Klin Exp Ohren Nasen Kehlkopfheilkd 198 361 1971
20 Foldi, M Gellert A Kozma M Poberai M Zoltan O T and Csanda E New contributions to the anatomical connections of the brain and the lymphatic system Acta Anat 64 498 1966
21 Bowsher D Pathways of absorption of protein from the cerebrospinal fluid An autoradiographic study in the cat Anat Rec 128 23 1957
22 Frederickson R G and Low F N Blood vessels and tissue space associated with the brain of the rat Am J Anat 125 123 1969
23 Cserr H F Relationship between cerebrospinal fluid and interstitial fluid of brain Fed Proc 33 2075 1974
24 Tuke J B Morrison Lectures on Insanity Edinburgh Med J 39 673 1894
25 Foldi M Csanda E Simon N, Obál F, Schneider I Dobranovics I Zoltán O T, Kozma M and Poberai M Lymphogenic haemangiopathy "Prelymphatic pathways in the wall of cerebral and cervical blood vessels Angiology 5 250 1968
26 Foldi M Csillik B and Zoltán O T Lymphatic drainage of the brain Experientia 24 1283 1968
27 Foldi, M Szenes T Kahán A Thury G and Zoltán O T Experimental lymphography by means of a subarachnoidal injection of Lipiodol ultrafluid Experientia 23 455 1967
28 Casley Smith J R Foldi Borcsök E and Foldi M The prelymphatic pathways of the brain as revealed by cervical lymphatic obstruction and the passage of particles British Journal of Experimental Pathology 57 179 1976
29 Kozma M Zoltán O T and Csillik B Die anatomischen Grundlagen des pralymphatischen Systems im Gehirn Acta Anat 81 409 1972
30 Csanda E Untersuchungen zur pralymphatisch lymphatischen zerebro zervikalen Dramage bahn Folia Angiol 22 79 1974
31 Csanda E Szucs A Dobranovics I Saal, M and Oswald A Hirnschadigungen infolge von Beta Strahler Yttrium 90 Weitere Untersuchungen zur Frage der pralymphatisch lymphatischen Drainage bahn aus der Hirnsubstanz, Folia Angiol 22 172, 1974
32 Oehmichen M Experimental studies on kinetics and functions of mononuclear phagocytes of the central nervous system Acta Neuropathol 6 285 1975
33 Selzer H Gruninger H Harrer G and Pilz, P Tierexperimentelle Untersuchungen zur Beeinflussung der lymphatischen cerebro cervicalen Drainagebahn durch Ultraschall Acta Neuropathol 33 201 1975
34 Foldi M Csillik B Várkonyi T and Zoltán O T Lymphostatic cerebral hemangiopathy Ultrastructural alterations of the brain blood capillaries after blockage of cervical lymph drainage Vasc Surg 2 214 1968
35 Várkonyi, T Csillik, B Zoltán O and Foldi, M Uber die feinstrukturellen Veränderungen im Grosshirn bei der lymphogenen Enzephalopathie der Ratte Beitr Pathol Anat 139 344 1969
36 Courtice F C and Simmonds W J The removal of protein from the subarachnoid space Aust J Exp Biol. Med Sci. 29 255 1951
37 Casley Smith J R L Donoghue P J and Crocker K W J The quantitative relationships between fenestrae in jejunal capillaries and connective tissue channels Proof of tunnel capillaries, Microvasc Res 9 78 1975
38 Foldi M Letter to the Editor Lancet 2 930 1975
39 Foldi M Várkonyi, T Joó F Csillik B and Zoltán O T Increased permeability of the blood brain barrier in lymphostatic encephalopathy Angiologica 6 275 1969
40 Foldi M Csanda, E Obál F and Zoltán O T Cerebral oedema as a consequence of experimental cervical lymphatic blockage Angiologica 5 55 1968
41 Foldi, M Karády I Horpácsy G Sonkodi, S Otlecz A and Sági I Lysosomal events in experimental lymphogenic encephalopathy Their treatment with pantothenic acid and pyridoxine Med. Exper 18 156 1968
42 Foldi M Csanda E Obál, F Madarász I Szeghy G and Zoltán O T Uber die Wirkungen der Unterbindung der Lymphgefasse und Lymphknoten des Halses auf das

material The perivascular space is the commencement of the lymph path which leads from the cell* to the main lymphatics of the head and neck [24] Our results [2] and those of others[29 33] have brought evidence that Tuke s description holds true and clarifies the details of the prelymphatic-lymphatic (hemangiolymphatic) drainage pathway

After intracerebral injection carbon could be traced (1) at the site of injection (2) in the adventitial spaces *inside* the skull (3) in the adventitia of the carotid artery *outside* the skull (4) in the lumina of vasa lymphatica vasorum situated in the wall of the *carotid artery* and (5) finally in the submandibular lymph node [2]

The same could be shown by using other tracers ferritin [45] monocytes [5] degraded brain tissue and oil After surgical occlusion of the cervical lymphatics an ascending stasis develops leading to a dilatation of the entire lymphatic and prelymphatic system as far as the basement membranes of cerebral blood capillaries [26] [35]

Courtice and Simmonds in 1951 injected into the cisterna magna of the cat dye labelled plasma protein As only 5 4 per cent of the injected amount of the dye protein entered the lymphatics and by far the greatest amount was removed by direct absorption into the blood it was concluded that the lymphatics do not play a major role in the absorption of CSF This conclusion is in my eyes responsible for the repression of the knowledge of connections between the brain and the lymphatic system in modern medicine But this view is a fallacy The significance of a pathway cannot be judged by the amount of materials transported through it per unit of time By comparing the lymph flow of the thoracic duct (two liters per day) with the cardiac output it would be tempting to ascribe no practical importance to the former in the circulation of body fluids *Only by studying the consequences of regional lymph blockages can conclusions be drawn concerning the functional significance of the lymphatic drainage* The consequences of cervical lymph blockage clearly demonstrate that although proteins certainly leave the intracranial site mostly through blood vessels and are partly disposed of by cellular uptake and degradation lymphatic drainage is vital too Just one example from another organ should illustrate this approximately 8 mg /min /100 G tissue albumin are reabsorbed by the fenestrated blood capillaries in the cat jejunum which is contrasted to only 1 mg transported by the lymphatics Nevertheless lymphatic blockage will induce lymphedema and lymphostatic enteropathy

Although both brain tissue proper and CSF are connected to the lymphatic system it is by no means justified to call CSF the lymph of the brain —it is as misleading as it would be to call the fluid inside the peritoneal cavity the lymph of the abdominal viscera

The mere fact that surgical lymphatic blockage of an organ results in a disease is the experimentum crucis proving that normal lymphatic drainage is a basic requirement of its normal functioning In the past 13 years the consequences of cervical lymphatic blockage resulting in lymphostatic encephalopathy were reported in a large series of papers [s] [s] [s] After this surgery perivascular Virchow Robin spaces dilate and contain a large amount of protein This cerebral lymphostatic hemangiopathy also involves blood capillaries mainly those possessing basement membrane labyrinths [6] There is some astrocytic edema Cerebral edema may result in a symmetrical herniation of the cisterna ambiens and in a protrusion of the vermis [2] Retinal and papillary edema and that of the optic nerve develop Behavior is altered apathy decreased motility extinction of learned behaviour and a diminished ability to learn have been described Convulsion threshold decreases The EEG shows marked pathological alterations A corresponding entity has been described in the human as well [3 3 5]

Blood vessels are playing an overwhelming role in the reabsorption of water and small molecules both from the brain tissue and from CSF Certainly even protein molecules are mainly drained by this route A relatively small but nevertheless vital protein clearance takes place from the cranial cavity by the lymphatic system (a) through perineuro lymphatic and (b) hemangio lymphatic pathways As there are no lymphatics in the brain the connection between the intracranial site and the lymphatics is accomplished by prelymphatics

The functional importance of any given regional lymphatic system can by no means be assessed by measuring lymph flow and lymphatic protein output and by comparing these data to blood flow and to the amount of protein transported from the tissues by the blood vessels The only reasonable approach to this problem is the study of the morphological and functional consequences of an experimental lymphatic blockage As cervical lymphatic blockage leads to the syndrome of lymphostatic encephalopathy exactly as hepatic lymph blockage or cardiac lymph blockage e g to lymphostatic hepatopathy and cardiomyopathy respectively it is justified to ascribe a role of fundamental importance to prelymphatic lymphatic drainage of the brain both in health and disease

Pure lymphostatic diseases are not as common as various pathological processes in which lymphatic load is increased and at the same time lymphatic drainage is partly or totally failing I have called this state safety valve insufficiency of lymph drainage it is characterized by massive cell death and has been demonstrated to play an important role in diseases of various organs (liver kidney etc) Evidence has been presented that also in the brain various experimental lesions are much more severe if combined with cervical lymphatic blockage [6]

Our papers on the prelymphatic-lymphatic drainage of the brain and on lymphostatic encephalopathy have only found a minimal resonance until now According to Stent data that cannot be transformed into a structure congruent with canonical knowledge are a dead end That is they remain meaningless until a way be shown to transform them into a structure that is congruent with the canon Perhaps this annotation will help to give the necessary insight into the viewpoints of lymphology and convince both physiologists and clinicians that the time is ripe to dispose of some cherished dogmata and accept the reality that without taking lymphatic drainage of the brain into consideration understanding and analysis which concern both normal function and states of disease must remain incomplete

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The amount of protein and water per unit of time which await lymphatic transport

* i e the brain tissue

REFERENCES

1 Foldi M Physiologie und Pathophysiologie des Lymphgefasssystems *in* Meesen H ed Handbuch der allgemeinen Pathologie Vol 3 part 6 Berlin Heidelberg New York 19 2 Springer Verlag
2 Casley Smith, J R The lymphatic system in inflammation *in* Zweifach B W Grant L and McCluskey R T, editors The inflammatory process New York/London 1973 Academic Press Inc p 161
3 Foldi, M Diseases of lymphatics and lymph circulation Springfield 1969 Charles C Thomas, Publisher
4 Foldi M Kluken N and Collard M Praxis der lymphgefass und Venenerkrankungen Stuttgart 1974 Gustav Fischer Verlag
5 Foldi M Physiologie des lymphgefasssystems Angiologica 8 1 19 1
6 Witte S Goldenberg D M and Schricker K T Die Ausbreitung von Fluorescenzfarbstoffen in der Hamsterbackentasche Z Exp Med 148 2 1968
7 Foldi M Lymphostatische Krankheitsbilder Herz Kreislauff 2 21 19 0
8 Brown P Albumin connective tissue and the blood brain barrier Bull Johns Hopkins Hosp 108 200 1961
9 Wagner H J Pilgrim C and Brandl J Penetration and removal of horseradish peroxidase injected into the cerebral fluid Role of cerebral perivascular spaces endothelium and microglia Acta Neurophathol (Berl) 27 299 19 4
10 Yoffey J M and Courtice F C Lymphatics lymph and the lymphomyeloid complex London/New York 19 0 Academic Press Inc
11 Lance E M A functional and morphologic study of intracranial thyroid allografts in the dog Surg Gynecol Obstet 125 529 196
12 Lance E M A functional and morphological study of intracranial parathyroid allografts in the dog Transplantation 5 14 1 196
13 Casley Smith J R The actions of the benzo pyrones on the blood tissue lymph system Folia Angiologica 19 6 24 7 19 6
14 Foldi M and Foldi Borcsok E Lymphostase und Vitamine Angiologica 10 101 1973
15 Foldi Borcsok E and Foldi, M Lymphedema and vitamins Am J Clin Nutr 26 185 1973
16 Key A and Retzius, G Studien in der Anatomie des Nervensystems und des Bindégewebes Stockholm 18 6 P A Norstedt & Soner
17 Iwanow G Uber die Abflusswege aus den Subarachnoidal raumen des Gehirns und Ruckenmarks und uber die Methodik ihrer intravitalen Untersuchung Z Exp Med 64 356 1928
18 Field E J and Brierley J B The retro orbital tissue as a site of outflow of cerebrospinal fluid Proc R Soc Med 42 44 1949
19 Arnold W Nitze H R and Ritter R Anatomical relations between the cerebrospinal fluid (CSF) and the lymphatic system in the region of the head and neck Arch Klin Exp Ohren Nasen Kehlkopfheilkd 198 361 19 1
20 Foldi M Gellert A Kozma M Poberai, M Zoltan O T and Csanda E New contributions to the anatomical connections of the brain and the lymphatic system Acta Anat 64 498 1966
21 Bowsher D Pathways of absorption of protein from the cerebrospinal fluid An autoradiographic study in the cat Anat Rec 128 23 195
22 Frederickson R G and Low F N Blood vessels and tissue space associated with the brain of the rat Am. J Anat 125 1 3 1969
23 Cserr H F Relationship between cerebrospinal fluid and interstitial fluid of brain Fed Proc 33 2075 1974
24 Tuke J B Morrison Lectures on Insanity Edinburgh Med J 39 6 3 1894
25 Foldi M Csanda E Simon N Obál F, Schneider I Dobranovics I, Zoltán O T, Kozma M and Poberai M Lymphogenic haemangiopathy "Prelymphatic pathways in the wall of cerebral and cervical blood vessels Angiology 5 250 1968
26 Foldi M Csillik B and Zoltán O T Lymphatic drainage of the brain Experientia 24 1283 1968
27 Foldi, M Szenes T Kahán A Thury G, and Zoltán O T Experimental lymphography by means of a subarachnoidal injection of Lipiodol ultrafluid Experientia 23 455 1967
28 Casley Smith J R Foldi Borcsok E and Foldi, M The prelymphatic pathways of the brain as revealed by cervical lymphatic obstruction and the passage of particles British Journal of Experimental Pathology 57 179 19 6
29 Kozma M Zoltán O T and Csillik B Die anatomischen Grundlagen des pralymphatischen Systems im Gehirn Acta Anat 81 409 1972.
30 Csanda F Untersuchungen zur "prálymphatisch lymphatischen zerebro zervikalen Drainage bahn " Folia Angiol. 22 29 1974
31 Csanda E Szűcs A Dobranovics I Saal M and Oswald A Hirnschadigungen infolge von Beta Strahler Yttrium 90 Weitere Untersuchungen zur Frage der pralymphatisch lymphatischen Drainage bahn aus der Hirnsubstanz, Folia Angiol. 22 152, 1974
32 Oehmichen M Experimental studies on kinetics and functions of mononuclear phagocytes of the central nervous system Acta Neuropathol 6 285 1975
33 Selzer H Grüninger H Harrer G and Pilz P Tierexperimentelle Untersuchungen zur Beeinflussung der lymphatischen cerebro-cervicalen Drainagebahn durch Ultraschall Acta Neuropathol. 33 201 1975
34 Foldi M Csillik B Várkonyi T and Zoltán, O T Lymphostatic cerebral hemangiopathy Ultrastructural alterations of the brain blood capillaries after blockage of cervical lymph drainage Vasc Surg 2 214 1968
35 Várkonyi T Csillik B Zoltán O and Foldi, M Uber die feinstrukturellen Veränderungen im Grosshirn bei der lymphogenen Enzephalopathie der Ratte Beitr Pathol Anat 139 344 1969
36 Courtice F C and Simmonds W J The removal of protein from the subarachnoid space Aust J Exp Biol Med. Sci 29 255 1951
37 Casley Smith J R L Donoghue P J and Crocker K W J The quantitative relationships between fenestrae in jejunal capillaries and connective tissue channels Proof of tunnel-capillaries" Microvasc Res 9 78 19 5
38 Foldi, M Letter to the Editor Lancet 2 930 1975
39 Foldi, M Várkonyi T, Joó F Csillik B and Zoltán O T Increased permeability of the blood brain barrier in lymphostatic encephalopathy Angiologica 6 275 1969
40 Foldi, M Csanda E Obál F and Zoltán O T Cerebral oedema as a consequence of experimental cervical lymphatic blockage Angiologica 5 55 1968
41 Foldi M Karády I Horpácsy G Sonkodi S Otlecz A and Sági I Lysosomal events in experimental lymphogenic encephalopathy Their treatment with pantothenic acid and pyridoxine Med Exper 18 156 1968
42 Foldi M Csanda E Obál F Madarász I Szeghy G, and Zoltán O T Uber die Wirkungen der Unterbindung der Lymphgefasse und Lymphknoten des Halses auf das

Zentralnervensystem im Tierversuch Z Exp Med **137** 483 1963
43 Foldi M Obál F Madarász I Zoltán O T and Csanda I Die Wirkung der Unterbindung der Lymphgefasse und Lymphknoten des Halses auf das Zentralnervensystem Z Exp Med **138** 26 1964
44 Foldi M Zoltán O T Obál F and Madarász I Die Wirkung der Unterbindung der Lymphgefásse und Lymphknoten des Halses auf das Zentralnervensystem Z Exp Med **138** 43 1964
45 Foldi M Zoltán O T Obál F Madarász I and Lehotai L Die Wirkung der Unterbindung der Lymphgefasse und Lymphknoten des Halses auf das Zentralnervensystem Z Exp Med **138** 185 1964
46 Földi M Obál F Madarász I Dobozi A and Zoltán O T Veränderungen des Gamma amino Buttersäure gehaltes verschiedener Hirnstrukturen bei der lymphogenen Enzephalopathie Angiologica **3** 360 1966
47 Foldi M Várkonyi T Csillik B and Zoltán O T Lymphostatic retinal hemangiopathy Experientia **26** 67 1970
48 Foldi M Csanda F Zoltán O T and Dobronovics I Oedema of the optic nerve and the retina as a consequence of experimental cervical lymphatic blockage Angiologica **4** 341 1967
49 Foldi M Increased permeability of the blood brain barrier in lymphostatic encephalopathy An electron microscopic study Angiologica **6** 318 1969
50 Foldi M Joó F Takács O Varga L Domjan C Börcsök E Rott S Rosta M Zoltán O T and Csillik B Collapse of the blood brain barrier in lymphostatic cerebral hemangiopathy and in triethylene poisoning Med Exp **19** 312 1969
51 Foldi M Szeghy G Polgar J Sonkodi S and Gyori I Increased permeability of the blood aqueous barrier in lymphogenic encephalopathy Angiologica **6** 313 1969
52 Obál F Madarász I Zoltán O T and Foldi M Effect of the disturbance of cervical lymph drainage (lymphostatic encephalopathy) upon the EEG and cerebral functions *in* Results in neuroanatomy neuroendocrinology neurophysiology and behaviour Budapest 1973 Neuropathol 6 215 Akademiai Kiado
53 Foldi M Kahán A Polgár J Szeghy G Börcsök E Liptak K and Maurer M Fundus lymphostaticus und Kopfschmerzen Arch Klin Med **216** 5? 1969
54 Foldi M Simon M Borcsök E Maurer M and Lehotai L Characteristic striation and ridge pattern of the cervical skin in lymphogenic encephalopathy Acta Paediatr Acad Sci Hung **9** 267 1968
55 Foldi M Csanda E Toth K Obál F Madarász I Romhányi G Varga L and Wagner A Uber das Melkersson Rosenthal Miescher Syndrom Murch Med Wschr **106** 296 1964
56 Foldi M Obál F Kahán A Wagner A Csanda E and Börcsök E Lymphogene Enzephalopathie Ein neues Krankheitsbild und seine Behandlung Acta Paediatr Hung **8** 171 1967
57 Foldi M Borcsök E Gyori I Kahán A Maurer M Obál F Polgár J, Stepper M Szabon J, Wagner A, and Zoltán O T Uber die Insuffizienz des zervikalen Lymphgefasssystems die Trias Lymphostatische Enzephalopathie lymphostatische Ophthalmopathie–transLymphdrainage des Hautgewebes des Halses Herz Kreislauff **2** 375 1970
58 Foldi M Gyori I Börcsök F Maurer M and Zoltán, O T Lymphogene Enzephalopathie lymphogene Ophthalmopathie und Hypofunktion des Lymphgefasssystems des Hautgewebes des Halses Med Klin **65** 10?? 1970
59 *Földi M Obál F Szabon J and Borcsok E* Effect of tonsillectomy on the EFG Acta Med Acad Sci Hung **26** 317 1969
60 Foldi M Zoltán O T Sonkodi S Sebök S Domonkos H Fekete F and Deak I Lymphogenic encephalopathy and brain edema Angiologica **5** 372 1968
61 Foldi Börcsök E and Foldi M Untersuchungen bei der lymphostatischen Enzephalopathie des Menschen Folia Angiol **20** 13 1972
62 *Földi Börcsök E and Foldi M* Lymphostatic encephalopathy and vitamins Am J Clin Nutr **26** 696 19?
63 Casley Smith J R Foldi Borcsök E and Foldi M Fine structural aspects of the influence of lymphatic blockage on cold injury of the brain and skin and the effects of benzo pyrones Drug Res 19 6 (In press)
64 Stent G H Prematurity and uniqueness in scientific discovery Sci Am **227** 84 1972
65 Oehmichen M Demonstration of corpuscular and cellular tracers in the lymphatic system Lecture Third International Symposium on Multiple Sclerosis Schonmunzach 1974
66 Leonhardt H Uber die Blutkapillaren und perivaskulären Strukturen der area postrema des Kaninchens und über ihr Verhalten im Pentamethylentetrazolkrampf Z Zellforsch Mikrosk Anat **76** 511 1967
67 Hauck G Physiology of the microvascular system Angiologica **8** 236 1971

Labetalol, an α- and β-adrenergic blocking drug in the treatment of hypertension

The usefulness of beta adrenergic blocking drugs in the treatment of hypertension is well established although their mechanism of action remains controversial Labetalol is a drug with both alpha and beta adrenergic blocking actions which has recently been used in the treatment of hypertension Labetalol is effective when given by mouth and does not have the adverse respiratory effects occasionally encountered with propranolol Labetalol is particularly suited for intravenous use in hypertensive emergencies In a series of ?0 severely hypertensive patients three of whom were in the malignant phase intravenous labetalol 100 to 125 mg (1 5 to 2.0 mg /Kg) given either as a single bolus or by injection over 10 minutes caused an immediate fall in blood pressure from a mean of 196/127 mm Hg to 149/99 mm Hg 5 minutes after

completing the injection maintained at a mean of 160/10? mm Hg three hours later The effect continued up to 24 hours in four patients Severe hypotension was not observed in recumbency but postural hypotension was common and patients were allowed up and about initially only under supervision Other side effects were rare but in three patients with a very steep fall in pressure there was transient nausea pallor and sweating Labetalol caused significant reduction in heart rate without frank bradycardia together with correlated falls in plasma concentrations of angiotensin II and aldosterone All of these changes were most obvious in those patients with initially high plasma angiotensin II concentrations In five patients a direct cross-over comparison was made of labetalol 100 to 125 mg against propranolol 10 mg both drugs being given intravenously Labetalol caused immediate clear reductions in blood pressure propranolol did not By contrast propranolol was more effective in reducing pulse rate and plasma angiotensin II than was labetalol. Thus the principal mechanism of the acute blood pressure fall caused by labetalol seems to be alpha adrenergic blockade leading to peripheral vasodilation However beta blockade effects such as reduction in heart rate and plasma angiotensin II are no doubt valuable supplementary actions.

Labetalol should be particularly suited to the treatment of hypertension associated with catecholamine excess. In one patient experiencing a hypertensive crisis with excessive amounts of catecholamine metabolites in the urine following the withdrawal of clonidine 150 mg of labetalol intravenously reduced blood pressure from 232/1 0 to 168/122 mm Hg within 5 minutes, and a continued slow fall occurred in the next hour to 1?0/95 mm Hg

In pheochromocytoma oral labetalol in doses ranging from 600 to 6 400 mg daily has been successfully employed for the relief of hypertension dysrhythmias headaches sweating and cutaneous pallor before operation and also in a case of metastasizing pheochromocytoma with multiple secondary deposits Given by intravenous infusion across operation for the removal of pheochromocytoma labetalol prevented dangerous increases of blood pressure while the tumor was being dissected and there was no precipitous fall in pressure as it was excised.

On present evidence labetalol seems a promising addition to the antihypertensive pharmacopoeia and is worthy of more extensive trial

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REFERENCES

1 Prichard B N C Boakes A J Thompson F D and Joekes A M Some haemodynamic effects of compound AH5158 compared with propranolol propranolol plus hydrallazine and diazoxide the use of AH5158 in the treatment of hypertension Clin Sci Mol. Med. 48(Suppl 2) 9 19?o
2 Rosei, E A., Brown J J Lever A F Robertson J I S and Trust P M Intravenous labetalol in severe hypertension Lancet 2 1093 19 5
3 Rosei E A Brown J J., Fraser R Lever A F Morton J J Robertson A M Robertson J I S., and Trust P M The treatment of phaeochromocytoma and of clonidine withdrawal hypertension with labetalol, Br J Clin Pharmacol 19 6 (In press)
4 Rosei, E A Brown J J Fraser R Lever A F Morton J J Robertson J I S and Trust P M The effects of intravenous labetalol on blood pressure angiotensin II and aldosterone in hypertension comparison with propranolol Clin Sci. Mol Med 19?6 (In press)
5 Skinner C Gaddie J and Palmer K N V Comparison of intravenous AH5158 and propranolol in asthma Br Med J 2 59 19?5
6 Hansson L. and Hunyor S N Blood pressure overshoot due to acute clonidine (Catapres) withdrawal studies of arterial and urinary catecholamines and suggestions for management of the crisis Clin Sci Mol Med. 45(Suppl 1) 181 19?3

Of home cardiac care

The cost and emotional and psychic stress associated with care of the cardiac patient and also to the patient s family can be tremendous The recent trends toward hospital care and expensive and hazardous diagnostic and therapeutic procedures in the management of patients with heart disease are excessive and unnecessary These trends have never been fully evaluated by unbiased methods or people So why are they permitted to be used? There is a great deal of attention directed at satellite clinics small community hospitals, and rural and community medicine But what about management of the patient at home? After all a home is a mini satellite clinic and hospital combined Unfortunately physicians are not trained adequately today for the practice of medicine in the home All new developments in the practice of medicine are designed for use in hospitals and large clinics But imagine what could have been done if the same amount of emphasis and effort funds and personnel had been devoted to improving the care of cardiac patients in the home The convenience of hospital practice for physicians in large urban or even rural areas is evident But what if there were many more well trained and dedicated physicians for home care supported with the necessary minimal facilities equipment and materials? With many more physicians home care would be the routine care and large clinics and hospitals would remain for

special indications Of course the hospitals and clinics would be less in number but high in quality By far the largest number of illnesses can be managed well or even better in the home The care of the cardiac patient in the home can be good and hospital care is of questionable superiority [3] During the last quarter century in spite of much effort and expenditure of a great deal of funds the life expectancy of Americans has not increased nor has the incidence of deaths from cardiac disease declined for various age groups So what about the present trends in the care of the cardiac patient? There is a need to train many more doctors to change the present influence of supply and demand Expenditure of time and effort and developments for home care would certainly improve happiness among sick people and their families and reduce the cost of medical care greatly The home (the mini satellite hospital) and the private office (the mini clinic) need emphasis in a study to improve medical care and decrease cost

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REFERENCES

1 Burch G E and Giles T D A study of the effectiveness of the coronary care unit South Med J 64 43 1971
2 Burch G E Oei H K and Dillenkoffer R L Survival in a coronary care unit South Med J 68 947 1975
3 Mather H G Morgan D C Pearson N G Read K I Q Shaw D B Steed G R Thorne M G Lawrence C J and Riley I S Myocardial infarction a comparison between home and hospital care for patients Br Med J 1 925 1976

Computerized tomography and intracerebral hemorrhage

Non traumatic intracerebral hemorrhage is a common medical problem and the diagnosis is usually suggested on clinical grounds by a combination of the acute onset of meningism (with or without loss of consciousness) an obvious neurological deficit present from the outset and blood in the cerebrospinal fluid A recent study of 100 consecutive cases seen at our hospital showed that 52 were due to a ruptured berry aneurysm 38 to primary (hypertensive) hemorrhage eight to ruptured arteriovenous malformation and two final cases to hemorrhage from a previously unsuspected tumor Early diagnosis of the presence of hematoma is necessary as in some cases removal of the blood clot may be of therapeutic benefit Knowledge of the underlying pathology may also allow the surgeon to safeguard the patient against further hemorrhage (by clipping the aneurysm excising the angioma etc)

Until recently these two aspects of diagnosis required cerebral angiography which in addition to its dangers has been shown to have an accuracy of under 70 per cent for hematoma localization

Since the introduction of computerized tomography (C T scanning) it has become simple to make the diagnosis as intracerebral blood clot having a higher photon absorption coefficient than the surrounding brain appears as a well demarcated white area In addition the shape and position of the hematoma allows accurate predictions to be made as to the underlying pathology In our study we reviewed the scans of the patients with non traumatic intracerebral hemorrhage without recourse to any clinical information (such as name age blood pressure and clinical history) All the patients in the study had their predictions confirmed by angiography or necropsy The results are given in Table I From this it can be seen that a diagnosis of aneurysm or primary intracerebral hematoma can be made with approximately 90 per cent accuracy However when the figures are viewed in the light of the true pathology (as demonstrated by angiography or necropsy) it can be seen that three out of a possible total of 38 primary intracerebral hematomas were missed Only one aneurysm was missed out of a possible total of 52 as this had produced a hematoma splitting upwards from the carotid termination into the head of the caudate nucleus a common site for primary hemorrhage The table also shows that although four out of five angiomas were correctly predicted a further four were diagnosed incorrectly There were two tumors in the series both of which had presented clinically as cases of intracerebral hemorrhage and neither were recognized from their scan

The scans in which the presence of an aneurysm had been predicted were now divided into four further groups

1 Aneurysms of the anterior cerebral complex (including the anterior communicating artery)

2 Aneurysms at the main branchings of the middle cerebral artery

3 Aneurysms of the internal carotid artery complex (pos

Table I C T scan based prediction of pathology underlying non traumatic intracerebral hemorrhage

Pathology	*No predicted*	*No correct*	*No missed*	*No confirmed in group*
Primary hematoma	39	35	3	38
Aneurysm present	56	51	1	52
Angioma	5	4	4	8
Tumor	0	0	2	2
Total	100	90	10	100

terior communicating artery aneurysms terminal carotid artery aneurysms and aneurysms of the proximal middle cerebral artery)

4 Other aneurysms

These results are given in Table II The accuracy varies from 100 per cent for aneurysms of the anterior cerebral complex to 66 per cent for those few hematomas associated with aneurysms of the internal carotid complex

In the clinical situation more information about the patient is available to the physician and it should be possible to improve on the figures quoted above Therefore where C T scanning is available the role of angiography in the diagnosis and management of non traumatic intracerebral hematoma can be redefined

1 *Cerebral angiography is no longer required for the diagnosis and localization of the hematoma itself*

2 It is required in the minority of cases where the underlying pathology remains in doubt after C T scanning

3 It will always be necessary to provide information about

Table II Accuracy of C T scanning for predicting aneurysm site

Aneurysm site	*No predicted*	*No correct*	*No missed*	*No confirmed in groups*
Anterior cerebral complex	27	27	0	27
Middle cerebral	24	20	0	20
Int carotid complex	6	4	1	5
Others	1	1	0	1

Posterior cerebral artery aneurysm

the local vascular anatomy when *surgery is planned for either* an aneurysm or an angioma

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REFERENCES

1 Hayward R D and O'Reilly G V A Intracerebral haemorrhage Lancet 1 1 19/6
2 *Perret G., and Nishioka H Cerebral angiography* J Neurosurg 25 98 1966
3 McKissock, W Richardson A. and Walsh L. Primary intracerebral haemorrhage Lancet II 683 1959
4 Paxton R and Ambrose J The E M I scanner Br J Radiol. 47 530 1974

Letters to the Editor

Warfarin binding in kwashiorkor

To the Editor

As part of a general program studying drug metabolism in protein calorie malnutrition (PCM) and because the drug is known to be exclusively albumin bound the binding of warfarin to normal and kwashiorkor serum was studied in vitro

The binding of ^{14}C warfarin (S A 23 mCi per m mole) to pooled kwashiorkor serum (albumin 2 3 Gm /100 ml) and normal serum (albumin 4 05 Gm /100 ml) was studied by equilibrium dialysis Five dialyses were performed for both sera at total warfarin concentrations of 1 3 5 and 10μg per milliliter Total bound and free drug concentrations were estimated with a Packard Tricarb liquid scintillation counter The results are shown in Table I where it can be seen that there is no significant difference ($p = > 0.2$) between the binding characteristics of the two sera

Many patients in developing countries contract rheumatic fever and subsequently present with advanced rheumatic valvular disease necessitating valve replacement In this hospital alone approximately 200 valve replacements are performed annually Many of the patients by virtue of late presentation suffer from cardiac cachexia and hypoalbuminemia It is therefore of some importance to know that the therapeutic action of warfarin is not accentuated in this situation Due attention must nevertheless be paid to the drug interactions known to alter the action of warfarin

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Table I The binding characteristics of warfarin to normal and kwashiorkor serum

Total concentration (μg/ml)	Normal serum (4 05 Gm /100 ml)	Kwashiorkor serum (2 3 Gm /100 ml)
1		
% Bound	89 4 ± 1 3	90 3 ± 2 3
% Free	10 6 ± 1 3	9 7 ± 2 3
	(87 7 ± 8 3)	(87 6 ± 2 2)
3		
% Bound	92 3 ± 1 1	94 0 ± 0 4
% Free	7 7 ± 1 1	6 0 ± 0 4
	(91 3 ± 11 8)	(102 3 ± 13 1)
5		
% Bound	90 4 ± 2 2	95 4 ± 0 3
% Free	9 6 ± 2 2	4 6 ± 0 3
	(73 4 ± 15 8)	(90 1 ± 5 4)
10		
% Bound	95 5 ± 1 6	95 2 ± 0 8
% Free	4 5 ± 1 6	4 8 ± 0 8
	(120 4 ± 2 1)	(93 1 ± 0 9)

The figures in parentheses represent the percentage recovery after dialysis

REFERENCES

1 O Reilly R A and Kowitz P E Studies on the coumarin anticoagulant drugs Interaction of human plasma albumin and warfarin sodium J Clin Invest 46 829 1967
2 Buchanan N and Eyberg C Equilibrium dialysis A new system South Afr Med J 48 1867 1974
3 Solomon H M and Schrogie J J The effect of various drugs on the binding of warfarin C to human albumin Biochem Pharmacol 16 2129 1967
4 Udall J A Clinical implications of Warfarin interactions with five sedatives Am J Cardiol 35 67 19

Venesection

To the Editor

I was interested to see in the March issue of the JOURNAL (91 275 1976) that Seely recommended the reintroduction of venesection for patients suffering from coronary disease I would welcome some practical instruction namely how much blood to take how often

The article mentions hypercholesterolemia where venesection might be beneficial What about other manifestations of coronary disease such as angina? Would hypertensive patients benefit? Could it be applied to patients after an infarct?

Dr Ester Torok
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Reply

To the Editor

In reply to Dr Torok s letter my opinion is that venesection should initially be tried only in the most favorable cases namely on patients with a moderate degree of hypercholesterolemia who can tolerate a reasonably large loss of blood then extending application as indicated by experience The reason for stressing a *moderate* degree of hyperlipidemia is that a severe degree of it probably indicates failure of the normal defense mechanism in which case venesection is likely to be of no avail and in its absence there is nothing to indicate that loss of blood may help to eliminate noxious substance

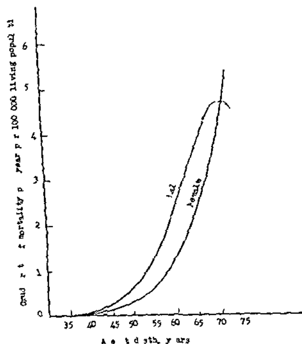


Fig 1 Mortality rates from hypertensive heart disease England and Wales 1973

The most interesting—and also the most difficult—question is wheth r venesection could con eivably benefit hypertensive patients The age distribution of mortality rates from hyper tensive heart disease (as hown in Fi 1 for England and Wales for the year 1973) is essentially similar to that for ischemi heart disease The crude mortality rates of women are substantially lower than of men in the younger age groups then run a parallel course with them from the age of menopause to early old age How ever the distance separating the ascending parallel sections of the curves is only about half of that obtaining in ischemic heart disease The possibility therefore exists that women derive some benefit from menstrual hemorrhages in both hypertensi e and ischemic heart disease but the benefit is less sub tantial in the former

It is interesting to note that the mortality rates of prem n opausal wc men from hypertensive renal disease are also lower than for men La tly the epidemiologic di tribution of hyper tension is similar to that of cardiovascular disease both are essentially diseases of ci ilization Hence the possibility that they ha e some factor of causation in common Perhaps a pathogen capable of interfering with holesterol metabolism also ha a noxious effect on the kidneys The distress of these may then give rise tc hyperten ion which in turn a gravates both cardiovascular and cerebrovascular disease

Summarizing, there is some rea on to b lieve that hyperten sives may benefit fr m venesection justifying perhaps a trial on a few consenting patients It would be interestin to know the results

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REFERENCES

1 The Registrar General s Statistical Review for England and Wales for the year 1973 London 1975 H M Stationary Office
2 Seely S Possible reasons for the comparatively high resistance of women to heart disease AM HEART J 91 275 1976
3 Page L B Epidemiologic evidence on the etiology of human hypertension and its possible prevention AM HEART J 91 527 1976

High resistance of women to heart disease

To the Editor

In a recent editorial Seely suggested that the apparent immunity of women to heart disease might be linked to the possibility that they have an alternative means of disposing of faulty cholesterol metabolites compared with men An alternative explanation might be that women have an inher ently stronger heart due to their reproductive capabilities. In the past families were considerably larger than the average family of today During pregnancy not only does the body weight in rease significantly but also considerable biochem ical changes occur This may impose significant stress and strain upon the heart for a considerable part of a woman s life and in order to withstand this the female heart may be inherently trong r By contrast the relative decline in family size in addition to the various aspects of increased liberation e g smoking alcohol, and work, may contribute to the recent increase in the incidence of ischemic heart disease

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Reply

To the Editor

The correlation between ischemic heart disease and preg nancies suggested by Drs Landman and Lavelle is an interest ing but so far unsubstantiated possibi ity The general obser vation that heart disease was less prevalent in the past wh n families were bigger or that it is still less prevalent in emergent countries notable for their fecundity is not a valid argument—not because it is untrue but because it applies to men as well as to women The only fact known with certainty is that ischemic heart disease is positively correlated with prosperity It is not yet known what exact aspect of prosperity is involved

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In reply to Dr Torok s letter my opinion is that venesection should initially be tried only in the most favorable cases namely on patients with a moderate degree of hypercholesterolemia who can tolerate a reasonably large loss of blood then extending application as indicated by experience The reason for stressing a *moderate* degree of hyperlipidemia is that a severe degree of it probably indicates failure of the normal defense mechanism in which case venesection is likely to be of no avail and in its absence there is nothing to indicate that loss of blood may help to eliminate noxious substances

patients with very low ejection fractions can be traced directly to differences in methodology used to obtain left ventricular cineangiograms Being one of the cardiologists who catheterized the patients for Drs Kay Mendez Zubiate and their colleagues I can state that we made thousands of selective left ventriculograms and forward angiograms often using the selective method for low ejection fractions, and in the past two years for patients with coronary artery disease we have used exclusively selective left ventriculograms Since 1971 selective left ventriculograms showed ejection fractions of 0 2 or less in 84 patients who had coronary artery disease and were later treated by surgical bypass grafting and/or aneurysmectomy Ten patients died during the surgical operation or during their stay in the hospital after operation In overly simplified arithmetic this is a mortality rate of 12 per cent but in the real world repetitions of the same operations would give a mortality rate between 5 8 per cent and 19 8 per cent (95 per cent confidence interval) Cohn Gorlin Cohn and Collins reported that in operations for coronary artery disease in patients with an ejection fraction below 0 3 there were five deaths out of ten operations which means there is a 95 per cent probability that repetitions of this surgery would yield a mortality rate between 19 per cent and 81 per cent

The value of experience is shown in reports from Dr Edward F Dunne the cardiac radiologist who read all the angiograms made by the cardiologists of the St Vincent Medical Center and many angiograms made by cardiologists of surrounding hospitals In six patients who had ejection fractions of 0 2 or less in selective left ventriculogram he also measured the ejection fraction from forward left ventriculograms with the following results (Table I)

Table I Ejection fractions in per cent

Patient	*Forward ventriculogram*	*Date*	*Selective ventriculogram*	*Date*
HS	20	6- ? 72	10	4 3 72
LR	20	10-2? 71	20	3 8-7?
VS	15	7 31 73	15	2 3 ?
FF	?0	10-23 72	15	7 20 73
CB	15	1? 16- 0	10	10 20-70
LS	15	5 9 73	15	5 9 73
Mean = 17 5% SD = 2 74 SE = 1 1?			Mean = 14 17% SD = 3 6 SE = 1 54	

Whether the ejection fraction was measured from forward or selective ventriculograms there was no difference of clinical or statistical significance (P = > 1) and the two methods could be used interchangeably

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REFERENCES

1 Ferlinz, J Herman M V Cohn P F and Gorlin R Comparison of selective left ventriculograms with levophase (forward) ventriculograms in patients with coronary artery disease AM HEART J 91 ?1 19 6
2 Goldstein A Biostatistics New York 1967 The MacMillan Company p 10
3 Ingle D J Principles of research in biology and medicine Philadelphia 1958 J B Lippincott Company Publisher p 89
4 Mullins, C B Leshin S J Mierzwiak V S Alsobrook H D and Mitchell J H Changes in left ventricular function produced by the injection of contrast media AM HEART J 83 373 1972
5 Kloster F E Friesen W G Green G S and Judkins M P Effects of coronary arteriograph on myocardial blood flow Circulation 46 438 1972
6 Gould K L Lipscomb K and Hamilton G W Physiologic basis for assessing critical coronary stenosis Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve Am J Cardiol 33 87 1974
7 Gould K L Hamilton G W Lipscomb K Ritchie J L and Kennedy J W Method for assessing stress-induced regional malperfusion during coronary arteriography Experimental validation and clinical application Am J Cardiol 34 557 1974
8 Mainland D Elementary medical statistics Philadelphia 1964 W B Saunders Company publishers p 28
9 Kay J H Dunne E Krohn B G Tsuji H K Redington J V Mendez A Dykstra P., and Magidson O Left ventricular excision exclusion or plication for akinetic areas of the heart J Thorac Cardiovasc Surg 59 139 1970
10 Kitamura S Echevarria M Kay J H Krohn B G Redington J V Mendez A Zubiate P and Dunne E F Left ventricular performance before and after removal of the noncontractile area of the left ventricle and revascularization of the myocardium Circulation 45 1005 1972
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12 Cohn P F Gorlin R Cohn L H and Collins J J Left ventricular ejection fraction as a prognostic guide in surgical treatment of coronary and valvular heart disease Am J Cardiol 34 136 1974
13 Herdan G Statistics of therapeutic trials New York 1955 Elsevier Publishing Company

Reply

To the Editor

We read with interest Dr Krohn s reactions to our recent paper in the AMERICAN HEART JOURNAL Apparently his objections to our study are of multifactorial nature One of his major criticisms appears to be that our findings might have been different if we had the necessary experience to appropriately analyze our own data The expertise that Dr Krohn s group possesses in interpreting ventricular cineangiograms (and which according to Dr Krohn we apparently lack) would then purportedly lead us to totally different conclusions—supposedly in agreement with Dr Krohn s assertion that the levophase (forward) and the selective ventriculograms can be used interchangably

Dr Krohn questions the design of our study by pointing out that a cross-over approach was not used when selective and levophase ventriculograms were performed Namely he would prefer that levophase ventriculograms were done first in half of the cases before selective ventriculograms or coronary

Valid evidence could be collected for example by examining hospital records to establish whether the mortality rate of multiparous women from coronary disease is less than that of childless women

If the suggested thesis is that the resistivity of women is due not to individual pregnancies but to the general fact that women are constituted to cope with them evidence for or against would be difficult to find In general terms however hopeful possibilities deserve more attention than hopeless ones If the high resistance of women to heart disease is attributable as I suggested to menstrual hemorrhages the hopeful possibility arises that hypercholesterolemic subjects may benefit from the easily applied therapeutic measure of venesection If the difference is attributed to the inherently stronger hearts of women nothing can be done to improve matters Genetic factors which are not under our control should not be invoked until the factors which are have been thoroughly explored and understood

Venesection has in fact been applied with reported beneficial effects to patients with severe angina

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REFERENCE

1 Burch G E and DePasquale N P The hematocrit in patients with severe myocardial infarction J A M A **180** 63 1962

Noisy floppy mitral valve

To the Editor

The recent report by Segall and subsequent letter by Lababidi[2] on murmurs of unusual intensity due to mitral valve prolapse prompts the addition of another case in a patient younger than the two previously reported or the one cited as the first described by Osler almost 100 years ago

H B was first seen at 3 years of age because her mother had heard repeatedly over a 2 month period a squeaky noise emanating from the child s chest This noise had been heard at a distance of 3 to 4 feet away from the child first noted when she jumped off her bed and thereafter following excitement exertion or forward bending There had been no symptoms of diminished cardiac reserve

Examination revealed a thin girl with a dolicocephalic head and high arched palate but no other stigma of the Marfan syndrome The mother was able to demonstrate the clearly audible noise heard 3 to 4 feet distant by having the girl exercise and lean forward in the standing position On further examination a loud late systolic whoop was heard at the apex on recumbency On sitting the intensity of the whoop lessened and a midsystolic click became audible Following exercise in the standing position the whoop was of maximal intensity and did not require the stethoscope for audibility

The chest x ray was normal The electrocardiogram showed a flat T wave in Lead III but this was upright 6 months later The echocardiogram showed evidence of prolapse of the posterior leaflet of the mitral valve A phonocardiogram showed a midsystolic click and a late systolic murmur of minimal intensity in the recumbent position

The girl has been examined three times over the past year Cardiac findings have been unchanged Periodic audibility of the murmur at a distance has still been noted by the mother

Undoubtedly these reports will stimulate additional recollections of similar experiences by others They afford a good example of the common aphorism that there are no new diseases only rediscovered old ones

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REFERENCES

1 Segall H N Autoauscultation in a patient with floppy mitral valve syndrome AM HEART J **91** 969 1976
2 Lababidi Z Floppy mitral whistle heard across the room AM HEART J **91** 825 1976
3 Osler W On a remarkable heart murmur heard at a distance from the chest wall Med Times Gaz Lond **2** 432 433 1880 Patient presented Medico Chirurgical Society of Montreal April 30 1880 Reported in Can Med Surg J **8** 518 1879 1880

Interchangeability of left ventriculograms

To the Editor

The paper Comparison of selective left ventriculograms with levophase (forward) ventriculograms in patients with coronary artery disease concludes that the two kinds of left ventriculograms cannot be used interchangeably This generalization is false because the design of the experiment from which it arose contains two fundamental errors

The first error lack of balanced design permits bias in comparing two procedures in the same sequence in the same individuals The first procedure may influence the results of the second chance differences in the subjects during the procedures may influence the outcome adaptation rather than the procedures may influence the results The authors hoped to overcome some of the bias by making the forward ventriculograms 60 minutes after the selective left ventriculograms and 30 minutes after the coronary angiograms To support this hope they referred to four studies which gave NO evidence that the depressing effects of Renografin 76 on the ejection fraction of atherosclerotic hearts disappear in 60 minutes The authors did not correct the bias by the common method which is to do each procedure first in half the cases and each procedure last in half the cases (cross over)

The second error in the design permits bias by assuming that physicians who measure a small number of forward left ventriculograms and thousands of selective left ventriculograms will measure both types with the same precision and accuracy

The paper also makes an invalid conclusion that comes from an error of fact The authors referring to the great success in operating on patients with extremely low ejection fractions reported by Drs Jerome Harold Kay A Michael Mendez and Pablo Zubiate as contrasted to their own 50 per cent mortality rate stated that Kay Mendez and Zubiate employ levophase (forward) ventriculograms for their left ventricular analysis and It is therefore quite possible that the interinstitutional differences in surgical survival of

patients with very low ejection fractions can be traced directly to differences in methodology used to obtain left ventricular cineangiograms.[7] Being one of the cardiologists who catheterized the patients for Drs Kay Mendez Zubiate and their colleagues I can state that we made thousands of selective left ventriculograms and forward angiograms often using the selective method for low ejection fractions, and in the past two years for patients with coronary artery disease we have used exclusively selective left ventriculograms Since 1971 selective left ventriculograms showed ejection fractions of 0 2 or less in 84 patients who had coronary artery disease and were later treated by surgical bypass grafting and/or aneurysmectomy Ten patients died during the surgical operation or during their stay in the hospital after operation In overly simplified arithmetic this is a mortality rate of 12 per cent but in the real world repetitions of the same operations would give a mortality rate between 5 8 per cent and 19 8 per cent (95 per cent confidence interval) Cohn Gorlin Cohn and Collins reported that in operations for coronary artery disease in patients with an ejection fraction below 0 3 there were five deaths out of ten operations which means there is a 9 per cent probability that repetitions of this surgery would yield a mortality rate between 19 per cent and 81 per cent

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REFERENCES

1 Ferlinz J Herman M V Cohn P F and Gorlin R Comparison of selective left ventriculograms with levophase (forward) ventriculograms in patients with coronary artery disease Am Heart J 91 721 1976

2 Goldstein A Biostatistics New York 196[illegible] The MacMillan Company p 10

3 Ingle D J Principles of research in biology and medicine Philadelphia 1958 J B Lippincott Company Publisher p 89

4 Mullins C B Leshin S J Mierzwiak V S Alsobrook H D and Mitchell J H Changes in left ventricular function produced by the injection of contrast media Am Heart J 83 373 1972

5 Kloster F E, Friesen W G Green G S and Judkins M P Effects of coronary arteriograph on myocardial blood flow Circulation 46 438 1972

6 Gould K L Lipscomb K and Hamilton G W Physiologic basis for assessing critical coronary stenosis Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve Am J Cardiol 33 87 1974

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10 Kitamura S Echevarria M Kay J H, Krohn B G Redington J V Mendez A Zubiate P and Dunne E F Left ventricular performance before and after removal of the noncontractile area of the left ventricle and revascularization of the myocardium Circulation 45 1005 1972

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Dr Krohn questions the design of our study by pointing out that a cross over approach was not used when selective and levophase ventriculograms were performed Namely he would prefer that levophase ventriculograms were done first in half of the cases, before selective ventriculograms or coronary

angiography While this is often a sound procedure it was not possible to implement it in our study Namely coronary arteriography *had* to be performed first in all cases as it served as the very criterion for the inclusion of patients into the study Further the selective ventriculogram was considered an essential part of the diagnostic procedure and had to be performed prior to the research phase of the study because our earlier data suggested that levophase cineangiograms may not be technically as satisfactory as the selective injections If a cross over design can not be performed however the experiment is statistically equally as valid if there is a solid prior evidence that the time allowed between the two procedures is of sufficient length to assure the subject s return to the base line state Dr Krohn claims that we give no evidence to this effect—i e that a pause of 60 minutes between the two ventriculograms might not be of sufficient length to remove the myocardial depressant effect of meglumine sodium diatrizoate (Renografin 76) Dr Krohn could not have digested our paper or reviewed the references that we cited very carefully when making such a statement In a carefully designed study Mullins and colleagues measured multiple left ventricular parameters (including the ejection fraction) before and after the intraventricular administration of Renografin 76 They found that *all values* returned to the control levels by *15 minutes* In a different study (also referenced in our paper) Cohn and associates have shown that the left ventricular ejection fraction in patients with coronary artery disease varies by no more than 4 per cent if sequential ventriculograms are performed only 30 minutes apart

We find Dr Krohn s statement that we might have introduced bias into our study because we purportedly lack the experience to analyze levophase ventriculograms both surprising and at the same time detrimental to the very thesis that Dr Krohn is trying to establish As reasonably competent investigators in the field of cardiovascular angiography we find no great mysteries in quantitatively analyzing the selective or levophase left ventriculograms If some recondite expertise or esoteric techniques (which according to Dr Krohn may somehow not be known to us) are required to analyze the levophase ventriculograms then the selective and levophase techniques are almost by definition vastly different in nature and should not be used interchangably on this basis alone

When referring to the high operative mortality rate of patients with very low ejection fractions (less than 30 per cent) we did not quote only our experience Numerous investigators report similar dismal operative results Since the completion of our manuscript further reports were published again demonstrating that very high operative mortality rates are seen in patients with valvular or coronary artery disease when left ventricular ejection fraction falls below 30 per cent These results are dramatically contrasted by the very low mortality rates of Kay and colleagues when operating on patients with extremely low ejection fractions (mortality rate of 12 per cent when ejection fraction is 20 per cent or less) Dr Krohn does not accept even a possibility that different methodologies used in determining the left ventricular ejection fraction (and therefore the preselection of different patient populations) may be one of the key reasons why these vast difference in surgical survival exist between his cardiovascular center on one hand and *every other institution* which performs similar procedures on the other He states that he made thousands of selective left ventriculograms and forward angiograms often using the selec e method for low ejection fraction Yet the reference that he uses to substantiate this claim[1] reveals that only *nine* patients were investigated in this study that all had levophase ventriculograms and that only some patients in this series had both methods performed in order to prove the *absence of mitral regurgitation*

We are mystified as to what conclusions is Dr Krohn trying to reach by calculating the 95 per cent confidence intervals for his and our surgical series If he is trying to make a point that his high limit (19 8 per cent) and our low limit (19 per cent) overlap—and that therefore the difference between the two series is really not all that significant—he is committing a statistical non sequitur To quote "Unfortunately there is a tendency among those unfamiliar with statistical methods to treat confidence limits inappropriately as bounds that enclose a proportion of the population This is a grave error For example it is erroneous in the case of the survival times to interpret the 95 per cent confidence limits as indicating that 95 per cent of the survival times are within these bounds The limits concern only the *mean* of the population from which the sample was selected The limits that embrace 95 per cent of survival times are quite another matter their determination involves knowledge of the *population* distribution of survival times

The final irony of Dr Krohn s communique must be the data that he presents on six of his patient who had low ejection fractions and levophase plus selective ventriculograms After questioning every conceivable aspect of our well documented study he offers these six patients collected over a *three year* period and unaccompanied by any details whatsoever about the methodologies used as proof that the two techniques can be used interchangably[1]

After all these points have been aired the inescapable conclusion (even without all the supporting data) still remains that if less than 100 ml of contrast medium is injected into the right side of the heart and then diluted in approximately 1 ml of blood that is normally contained in the lung the outline of the left ventricle simply *can not* be as precise (when this dilute dye passes through) as it becomes when a selective ventricular injection takes place Many investigators have long ago recognized the problems associated with levophase injections and some have called for the abandonment of this approach Apparently Dr Krohn himself must have reached similar conclusions because he states in his letter that in the past two years selective left ventriculograms were used exclusively by his group Why he therefore continues to insist that the two methods are interchangable is not at all clear to us

One final item It has by now been clearly demonstrated that patients with severe coronary artery disease and substantial left ventricular asynergy (i e generally the patients with the lowest ejection fractions) can be accurately characterized only with *biplane* left ventricular cineangiography and that single plane studies usually underestimate the left ventricular ejection fraction To what an extent this introduces yet further discrepancies into the reports by Dr Krohn s group (which apparently uses single plane angiography[1] [2]) is not clear

The findings of our study demonstrated that different methodologies can yield vastly divergent results in the same

patients. These findings also offered a very plausible explanation why surgical survival rates may differ to such a great extent between the various medical centers that are *all* highly qualified to perform coronary artery bypass surgery. Yet rather than allowing for the possibility that these factors just might be at play and therefore introducing at least a modicum of consensus into this very complex area of what to do with people whose hearts are just barely functional, Dr. Krohn finds it necessary to present frequently arbitrary, at times irrelevant, and occasionally totally erroneous arguments against our work.

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REFERENCES

1. Ferlinz, J., Herman, M. V., Cohn, P. F., and Gorlin, R.: Comparison of selective left ventriculograms with levophase ("forward") ventriculograms in patients with coronary artery disease, AM. HEART J. 91:771, 1976.
2. Cohn, P. F., Levine, J. A., Bergeron, G. A., and Gorlin, R.: Reproducibility of the angiographic left ventricular ejection fraction in patients with coronary artery disease, AM. HEART J. 88:713, 1974.
3. Colton, T.: Statistics in medicine, Boston, 1974, Little, Brown & Company, chap. 4, p. 136.
4. Mullins, C. B., Leshin, S. J., Mierzwiak, D. S., Alsobrook, H. D., and Mitchell, J. H.: Changes in left ventricular function produced by the injection of contrast media, AM. HEART J. 83:373, 197-.
5. Cohn, P. F., Gorlin, R., Cohn, L. H., and Collins, J. J.: Left ventricular ejection fraction as a prognostic guide in surgical treatment of coronary and valvular heart disease, Am. J. Cardiol. 34:136, 1974.
6. Oldham, H. N., Kong, Y., Bartel, A. G., Morris, J. J., Jr., Behar, V. S., Peter, R. H., Rosati, R. A., Young, G., Jr., and Sabiston, D. C.: Risk factors in coronary artery bypass surgery, Arch. Surg. 105:918, 1972.
7. Lea, R. E., Tector, A. J., Flemma, R. J., Johnson, W. D., Beddingfield, G. W., and Lepley, D., Jr.: Prognostic significance of a reduced left ventricular ejection fraction in coronary artery surgery (Abst.), Circulation 46(Suppl. II):II-49, 19--.
8. Yatteau, R. F., Peter, R. H., Behar, V. S., Bartel, A. G., Rosati, R. A., and Kong, Y.: Ischemic cardiomyopathy. The myopathy of coronary artery disease. Natural history and results of medical versus surgical treatment, Am. J. Cardiol. 34:520, 1974.
9. Hammermeister, K. E., Kennedy, J. W., Fisher, L., and Dodge, H. T.: Prognostic value of the ejection fraction in patients with valvular heart disease (Abst.), Circulation 52(Suppl. II):II-31, 1975.
10. Vlietstra, R. E., Assad-Morell, J. L., Elveback, L. R., Connolly, D. C., Frye, R. L., Danielson, G. K., and Wallace, R. B.: Survival prognosis in coronary artery disease with and without grafting (Abst.), Circulation 52(Suppl. II):II-142, 1975.
11. Kay, J. H., Redington, J. V., Mendez, A. M., Zubiate, P., and Dunne, E. F.: Coronary artery surgery for the patient with impaired left ventricular function (Abst.), Circulation 46(Suppl. II):II-43, 1972.
12. Kitamura, S., Echevarria, M., Kay, J. H., Krohn, B. G., Redington, J. V., Mendez, A., Zubiate, P., and Dunne, E. F.: Left ventricular performance before and after removal of the noncontractile area of the left ventricle and revascularization of the myocardium, Circulation 45:1005, 1972.
13. Colton, T.: Statistics in medicine, Boston, 1974, Little, Brown & Company, chap. 4, p. 12-.
14. Friedman, J. J., and Selkurt, E. E.: *In* Selkurt, E. E., editor: Physiology, Boston, 1963, Little, Brown & Company, chap. 18, p. 346.
15. Dodge, H. T., Hay, R. E., and Sandler, H.: An angiographic method for directly determining left ventricular stroke volume in man, Circ. Res. 11:739, 196-.
16. Sandler, H.: Dimensional analysis of the heart—A review, Am. J. Med. Sci. 260:56, 1970.
17. Hood, W. P., Jr., and Rackley, C. E.: *In* Grossman, W., editor: Cardiac catheterization and angiography, Philadelphia, 1974, Lea & Febiger, Publishers, chap. 11, p. 113.
18. Gentzler, R. D., Gault, J. H., Hunter, A. S., Liedtke, A. J., and Leaman, D. M.: Asymmetric left ventricular contraction in patients with previous myocardial infarction. Comparison of volume and dimensional characteristics derived from frontal and lateral cineangiograms, Circulation 48:352, 1973.
19. Vogel, J. H. K., Cornish, D., and McFadden, R. B.: Underestimation of ejection fraction with singleplane angiography in coronary artery disease. Role of biplane angiography, Chest 64:217, 1973.
20. Cohn, P. F., Gorlin, R., Adams, D. F., Chahine, R. A., Vokonas, P. S., and Herman, M. V.: Comparison of biplane and single plane left ventriculograms in patients with coronary artery disease, Am. J. Cardiol. 33:1, 1974.
21. Kay, J. H., Dunne, E., Krohn, B. G., Tsuji, H. K., Redington, J. V., Mendez, A., Dykstra, P., and Magidson, O.: Left ventricular excision, exclusion, or plication for akinetic areas of the heart, J. Thorac. Cardiovasc. Surg. 59:139, 1970.

Acute rheumatic fever and viral carditis

To the Editor:

I read Dr. C. Ward's editorial "Observations on the diagnosis of isolated rheumatic carditis" in the May, 1976 issue of the AMERICAN HEART JOURNAL with interest. I must note that as physicians we are not always at the mercy of the Jones Criteria. Although the distinction between acute rheumatic fever and viral carditis is indeed difficult, clinical acumen can help in the differentiation. I should like to make the following points.

1. Development of the murmur of aortic regurgitation certainly implies rheumatic origin since valvulitis of this type does not occur in viral myocarditis.

2. The murmur of mitral regurgitation, being more ubiquitous, can be seen in both viral and rheumatic carditis but in contradistinction to acute rheumatic fever is unlikely to occur in viral disease in the absence of significant cardiomegaly since in this disease mitral regurgitation is due to generalized myocarditis and is not purely valvular as it is in acute rheumatic fever.

angiography While this is often a sound procedure it was not possible to implement it in our study Namely coronary arteriography *had* to be performed first in all cases as it served as the very criterion for the inclusion of patients into the study Further the selective ventriculogram was considered an essential part of the diagnostic procedure and had to be performed prior to the research phase of the study because our earlier data[4] suggested that levophase cineangiograms may not be technically as satisfactory as the selective injections If a cross over design can not be performed however the experiment is statistically equally as valid if there is a solid prior evidence that the time allowed between the two procedures is of sufficient length to assure the subject s return to the base line state Dr Krohn claims that we give no evidence to this effect—i e that a pause of 60 minutes between the two ventriculograms might not be of sufficient length to remove the myocardial depressant effect of meglumine sodium diatrizoate (Renografin 76) Dr Krohn could not have digested our paper or reviewed the references that we cited very carefully when making such a statement In a carefully designed study Mullins and colleagues measured multiple left ventricular parameters (including the ejection fraction) before and after the intraventricular administration of Renografin 76 They found that *all values* returned to the control levels by *15 minutes* In a different study (also referenced in our paper) Cohn and associates have shown that the left ventricular ejection fraction in patients with coronary artery disease varies by no more than 4 per cent if sequential ventriculograms are performed only 30 minutes apart

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We are mystified as to what conclusions is Dr Krohn trying to reach by calculating the 95 per cent confidence intervals for his and our surgical series If he is trying to make a point that his high limit (19 8 per cent) and our low limit (19 per cent) overlap—and that therefore the difference between the two series is really not all that significant—he is committing a statistical non sequitur To quote Unfortunately there is a tendency among those unfamiliar with statistical methods to treat confidence limits inappropriately as bounds that enclose a proportion of the population This is a grave error For example it is erroneous in the case of the survival times to interpret the 95 per cent confidence limits as indicating that 95 per cent of the survival times are within these bounds The limits concern only the *mean* of the population from which the sample was selected The limits that embrace 95 per cent of survival times are quite another matter their determination involves knowledge of the *population* distribution of survival times

The final irony of Dr Krohn s communique must be the data that he presents on six of his patients who had low ejection fractions and levophase plus selective ventriculograms After questioning every conceivable aspect of our well documented study he offers these six patients collected over a *three year* period and unaccompanied by any details whatsoever about the methodologies used as proof that the two techniques can be used interchangably!

After all these points have been aired the inescapable conclusion (even without all the supporting data) still remains that if less than 100 ml of contrast medium is injected into the right side of the heart and then diluted in approximately 1 000 ml of blood that is normally contained in the lung the outline of the left ventricle simply *can not* be as precise (when this dilute dye passes through) as it becomes when a selective ventricular injection takes place Many investigators have long ago recognized the problems associated with levophase injections and some have called for the abandonment of this approach Apparently Dr Krohn himself must have reached similar conclusions because he states in his letter that in the past two years selective left ventriculograms were used exclusively by his group Why he therefore continues to insist that the two methods are interchangable is not at all clear to us

One final item It has by now been clearly demonstrated that patients with severe coronary artery disease and substantial left ventricular asynergy (i e generally the patients with the lowest ejection fractions) can be accurately characterized only with *biplane* left ventricular cineangiography and that single plane studies usually underestimate the left ventricular ejection fraction To what an extent this introduces yet further discrepancies into the reports by Dr Krohn s group (which apparently uses single plane angiography) is not clear

The findings of our study demonstrated that different methodologies can yield vastly divergent results in the same

Controversy in Cardiology The Practical Clinical Approach Edited by Edward K. Chung M.D. New York 19 6 Springer Verlag 299 pages. Price $29 80

This book reviews briefly 19 selected aspects in cardiology which the editor considers controversial. This reviewer finds it difficult to understand why all the subjects selected are controversial. There are always aspects of any subject about which there are differences of opinion and this is certainly so concerning the subjects reviewed in this book. Among the 19 cardiologic problems discussed are pacemakers in myocardial infarction, mobile intensive care units, antianginal agents, anticoagulant therapy, when to operate on congenital heart disease, cardiomyopathy, diagnostic criteria and classification and His bundle electrocardiography. The reader will find the book interesting and the contributors outstanding in their respective subjects. This is a useful and interesting book well worth studying.

Basic Circulatory Physiology By Daniel R. Richardson Ph.D. Boston 19 6, Little Brown & Company 1 9 pages

This short (about 179 pages) paperback book on basic circulatory physiology should interest undergraduate medical students and house staff. Those interested in the more profound aspects of the non-cardiac parts of the circulation will find the presentation to be extremely brief and not comprehensive. This book does however present some of the more important fundamental physiologic aspects of the circulation. The bibliographies are really too brief and by the author's selection fail to include those reports which consider the peripheral circulation from different points of view. The recommended references as is the general practice today fail to include some of the less recent classical publications. Nevertheless this brief book should interest readers and prove valuable provided they already have a good background in circulatory physiology and read the book critically.

Cardiac Diagnosis and Treatment second edition Edited by Noble O. Fowler M.D. Hagerstown Md 19 6 Harper & Row Publishers 1 150 pages. Price $42 50

Fowler's first edition of *Cardiac Diagnosis and Treatment* apparently has been well received to require a second edition and 14 additional chapters. The second edition with a new title and considerable expansion is a good clinically oriented book written by 20 contributors. The problems in diagnosis and treatment are clearly presented with many well selected illustrations and a fairly extensive bibliography appended to each chapter. The book is recommended to medical students and doctors in training as well as to the practicing physician. The book is also highly recommended for the private libraries of any physician who treats heart disease. Fowler has edited a good book, and now a comprehensive book and made a significant contribution to the field of textbooks on heart disease.

The Electrocardiogram By Emanuel Stein Philadelphia 19 6 W. B. Saunders Company 40 pages

This book consists of a series of electrocardiograms and legends presented to illustrate different applications in the interpretation of tracings. The approach is that of the author. He emphasizes the mean vector as obtained from the precordial leads and described by R. Grant. This approach has not been generally accepted and certainly oversimplifies the interpretation of the activation potential of the heart. This method of interpretation has also not been adequately correlated with clinical and autopsy data to justify its general use in clinical practice. The entire QRS complex in each of the V leads must be carefully inspected and considered individually and collectively when interpreting ECG tracings. Nevertheless the book lucidly presents Stein's approach to the study of ECGs and their interpretations. The illustrations clearly describe his thoughts. This is an interesting book on electrocardiography which should prove valuable to cardiologists.

Vectorcardiography 3 Edited by Irwin Hoffman and Robert I. Hamby Amsterdam 19 6 North Holland Publishing Company 220 pages Price $71 95

This book represents the proceedings of a symposium on clinical vectorcardiography held in New York City during May 1975. In light of the present interest in vectorcardiography (VCG) the availability of good direct writers (x y recorders) of the VCG cardiologists will find this book of considerable value. The contributors not only present their respective views of the subject of VCG but also summarize the present concepts in the field. The papers describe very well selected aspects of VCG which should interest readers who were not present at the symposium. The format of the book is essentially the same as that for other proceedings of symposia on any subject in medicine today.

Electrocardiographic Excursions By Leo Schamroth M.D., Philadelphia 19 6 J. B. Lippincott Company 158 pages Price $31 00

The author has published a series of electrocardiograms for study. The electrocardiograms represent various interesting clinical and cardiac problems. The illustrated electrocardiograms were selected to present an idea or problem in electrocardiographic interpretation and to challenge the reader. The title of each "study" ECG is intended to be cute or funny and to excite the reader's curiosity. Thus Schamroth has intentionally selected erotic tracings in order to be provocative and to teach the reader. This is an interesting book. Any cardiologist who opens the book will find himself carefully studying each ECG because of the interesting manner in which the titles are used and the interesting ECGs presented. This is a very good and instructive book.

Recent Advances in Critical Microcirculatory Research (8th EUROPEAN CONFERENCE ON MICROCIRCULATION Le Touquet 19 4) Edited by D. H. Lewis Basel 1975 S. Karger AG 3 8 pages Price $57 00

The series of conferences on the microcirculation has been consistently good. This publication like the others provides an opportunity for those who were not present to profit from the extensive deliberations. This publication is concerned with many aspects of the microcirculation e.g. capillary permeability, experimental and clinical rheology, sickling, regional blood flow, pharmacology, platelets, and others. The presentations are extremely brief and in some instances more like

3 Cardiomegaly occurring in the absence of murmurs is extremely unlikely to be rheumatic in origin but frequently occurs with viral cardiomyopathy

4 The electrocardiographic findings of viral myocarditis are usually much more pronounced and sometimes out of proportion to the clinical and x ray findings

These distinctive differences are at least as important as the Jones Criteria in distinguishing rheumatic and viral carditis The Jones Criteria are not mathematical formulae and only work in the presence of clinical expertise A cook book approach can not replace the competent clinician

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Reply

To the Editor

I wish to thank Dr Kloth for his letter and I am taking this opportunity to reply to it

I wrote the article in question to emphasise (1) the dangers of literal interpretation of the Jones Criteria and (2) the importance of making full use of current knowledge of the spectrum of viral heart disease when seeking the etiology of acute carditis

It is therefore difficult to understand Dr Kloth s criticism as his letter stresses these same two points Nevertheless although we apparently agree in principle the specific diag nostic clues he recommends may if taken at face value be misleading

1 As a rule aortic regurgitation occurring in the course of acute carditis certainly suggests a rheumatic etiology and my article did not suggest otherwise On the other hand we cannot afford to be dogmatic as viral aortic valvulitis has been documented

2 Cardiomegaly does occur in some patients with rheumatic carditis and a mitral systolic murmur The relev point here is that the Jones Criteria accept this combina (when no other cause is found) as evidence of rheum carditis

3 Although as I implied cardiomegaly without murmu unlikely to be rheumatic this fact is not acknowledged in th revised Jones Criteria

4 E C G changes in classical viral myopericarditis a marked and widespread but there is now evidence that vi heart disease often produces only minor S T and T wa changes[2, 3]

I am well aware that many clinicians apply the Jone Criteria with care On the other hand there is evidence i some published articles on the subject that this is not alwa done Jones originally published his diagno tic criteria in 19 The *American Heart Association* took it upon itself to modi these criteria in 1955 and to revise them in 1965 In the ensu g eleven years significant advances have been made in o understanding of viral heart disease Although one hesitates t *propose that the Jones Criteria be yet again updated* it is n unreasonable to suggest that these advances should be offi cially recognized

Dr Kloth quite rightly condemns the cookbook approa h to diagnosis—it is particularly dangerous when the recipe recommends the wrong ingredients'

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REFERENCES

1 Burch G E and Colclough H L Progres Coxsackie viral pancarditis and nephritis Ann Inter Med **71** 963 1969
2 Verel D Ward C and Rickards D F Electrocardio graphic changes in A England/42/72 influenza infectio in patients treated at home Proceedings of the British Cardiological Society *in* Br Heart J **36** 395 19 4
3 Verel D Warrack A J N Potter C Ward C and Rickards D F Observations on the A En land influenza epidemic A clinicopathological tudy Am Heart J **92** 290 1976

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Editorial

Perception of binary acoustic events associated with the first heart sound

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Statement of the problem general

The resolving power of the auditory apparatus permits discrete vibrations associated with cardiac activity to be perceived as one or more events The precise auscultatory resolution depends on many factors including frequency-amplitude products relative timings and both backward and forward masking If closely spaced a train of similar vibrations may not be individually separable and is perceived as a murmur If sufficiently separated other acoustically similar vibrations can be individually distinguished e g S -S at ordinary or slow heart rates In the absence of masking dissimilar vibrations usually can be easily resolved whether spaced closely (e g click-murmur) or widely (S -S)

Certain acoustic events in relation to S are considered potentially audible including (a) fourth heart sounds from the right and left ventricles (b) clicks associated with pulmonary artery and aortic ejection (c) early nonejection clicks and (d) the components of the S split associated with mitral and tricuspid closure (although the frequent phonocardiographic registration of S_1 as a train of several oscillations should raise a question as to exactly which vibrations might be M and T) The initial low frequency component of S_1 is assumed without proof to be inaudible

Irrespective of the vibratory combinations registered by conventional phonocardiography in normal adults and in most adult patients auscultators tend to discriminate only two discrete events associated with S_1 The question of what these two events are usually involves deciding among three choices (1) S_1 split components (2) S (which component?) + click and (3) S (which one or both ventricles?) + S (which component?)

Since some or all of these can be recorded it is clear that conventional phonocardiography often does not resolve by itself those of a series of vibrations actually perceived by the ear particularly when resolved into fewer discrete sounds than the number recorded

The question of audible S versus S split commonly is decided not by what the observer believes he hears but rather through the company it keeps and the built in biases of previous training Thus he may perceive an S only if he finds its palpatory counterpart the precordial A wave or if there are clinical data indicating a disease state which reduces ventricular compliance In truth this can be effective bedside practice since ancillary information is rarely absent But that such considerations bear on perceptual as well as interpretive biases is indicated by the remarkable

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abstracts This is an interesting publication which should interest physiologists and physicians and surgeons who treat diseases of the peripheral blood vessels

Recent Advances in Studies on Cardiac Structure and Metabolism Vol 7 *Biochemistry and Pharmacology of Myocardial Hypertrophy Hypoxia and Infarction* Edited by Peter Harris Richard J Bing and A Fleckenstein (Series Editor G Rona) Baltimore 1976 University Park Press 490 pages $39 50

The International Study Group for Research in Cardiac Metabolism has reviewed thoroughly the biochemistry and pharmacology of myocardial hypertrophy hypoxia and infarction These are three common and important diseases of the myocardium The discussions are basic and fundamental The material should interest biochemists physiologists and pharmacologists Physicians will find the presentations difficult but certainly worth their effort The myocardium is the pumping structure of the heart therefore a thorough knowledge of its functional cytology and gross anatomy is important for the cardiologist to know This seventh volume is another fine contribution to the medical literature by this excellent group of scientists

Books received

Underwater Medicine and Related Sciences A Guide to the Literature Volume 2 By Margaret F Werts and Charles W Shilling New York N Y 1976 Plenum Publishing Corp 647 pp Price $39 50

Surgery of the Heart Edited by J A Dyde and R E Smith New York N Y 1976 Plenum Publishing Corp 204 pp Price $19 50

Current Techniques in Extracorporeal Circulation By M I Ionescu and G H Wooler London England 1976 The Butterworth Group 547 pp Price 18 80 (Pounds)

Congenital Malformations of the Heart By Coor Lillebei New York N Y 1975 Grune & Stratton Inc and Medical and Scientific Pub 411 pp Price $32 50

Clinical Use of Drugs in Renal Failure By Anderson Gambertoglio and Schrier Springfield Ill 1976 Charles C Thomas 241 pp Price $19 50

Gibbon s Surgery of the Chest Third Edition By David C Sabiston Jr M D and Frank C Spencer M D Philadelphia Pa 1976 W B Saunders Company 1597 pp Price $67 50

Myocardial Revascularization A Surgical Atlas By Quentin R Stiles Bernard L Tucker George Lindesmith and Bert W Meyer Boston Mass 1976 Little Brown and Company 1• pp

Announcements

New Attitudes and Treatments for Hypertension

This one day course presented by the University of Texas Health Science Center at Houston Division of Continuing Education and Medical School will be held in Houston Texas on February 17 1977 The course is designed to discuss new developments in the treatment of the hypertensive patient including non drug measures and appropriate initial drugs the course is designed for physicians nurses and others who deal with hypertensive management For further information write Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

Conference on mild hypertension

A conference entitled Mild hypertension To treat or not to treat will be held at The Roosevelt Hotel New York City from February 9 through 11 1977 under the sponsorship of the New York Academy of Sciences For further information regarding this conference please contact Conference Department The New York Academy of Sciences 2 East 63rd St New York N Y 10021 Telephone (212) 838 0230

to establish time relationships in the cardiac cycle Thus for example a sound synchronous with presystolic precordial pulsation should be S and a much later sound preceding the carotid upstroke could be S or an early click However presystolic precordial displacement may not be palpated and both points of reference are them selves subject to perceptual errors particularly at rapid heart rates While such refinements cannot be neglected in practice they do not belong to the discussion of auscultatory perception Actual acoustic phenomena cannot be added to or subtracted from by observer biases They are heard or missed by the observer and their coun terparts are registered or missed by some kind of phonocardiograph Sound reaching the ear is not related to the auscultator s training how he perceives it and how he interprets it are [5]

Approaches to the problem investigations reported

Increasing numbers of phonocardiographic investigators are reporting registration of S in appreciable numbers of ostensibly normal per sons particularly older adults [1] Such sounds may pass filters with nominal peaks well above the audiometric threshold [6] suggesting that they might be audible Observer performance studies lend some support to that possibili ty although the observers in these studies might well be biased in favor of S audibility just as traditional auscultators (who have not yet reported observer performance studies) begin with the opposite bias

Recent observer performance studies utilizing three mutually blind auscultators and blind PCG interpretations and measurement con firmed and extended previous work in that the apparent audibility of recorded S s was not related to P R interval P S interval or relative amplitude of S When the PCG was indepen dently interpreted as showing S_1 splitting there was a tendency for S to be missed but this did not *reach* significance But S was easily heard in older subjects (mean age 50 0 years) and easily missed in younger subjects (mean age 31 2 years) Equally significant ($p < 005$) were the differ ences in the respective periods between S and the low frequency component (LFC) of S These were short (49 4 msec) for detected S and longer (70 0 msec) for missed S_4 With the principal S_4 frequencies averaging 20 Hz the mean S -LFC separation for detected S was almost exactly one cycle length Because the LFC and S are at comparable frequencies this raises a question of temporal acoustic summation which can increase perception of low frequency sound [1,3] Yet this remains hypothetical and does not prove S audi bility

Approaches to the problem work in progress

An alternate explanation which fits the facts may be stated as follows the significant S -LFC differences could be related to acoustic modifica tion of the early component of the S owing either to the proximity of S vibrations themselves or to physiologic factors associated with S e g the effect on S of differences in presystolic A V valve position owing to earlier or later atrial contribu tion to ventricular end diastolic filling and pres sure represented respectively by an earlier or later S Computer manipulations of taped heart sounds did not settle this question (owing to small numbers of subjects) but appeared to show *that if the* S_4-S (LFC) separation was increased the S_1 was perceived as a typically split S (i e sharp – sharp) if S -LFC was artificially decreased a dull – sharp sequence was per ceived with the same S vibrations

Significance of the problem

Auscultatory detection of S *if truly audible in* ostensibly normal persons and detection of S *of* borderline intensity are each of practical diag nostic importance if only because audibility *per se* and pathologic significance have been tradi tionally equated The effect of an audible and/or recordable S on the acoustic properties of S and the distinction of S from the first component of *an S split are of* both theoretic and practical importance in terms of observer performance and training of auscultators

REFERENCES

1. Ongley P A Sprague H B Rappaport M B., and Nadas A. S *Heart sounds and murmurs.* Clinical and phonocardiographic study New York 1960 Grune & Stratton Inc pp 16-36.
2. Luisada A A From auscultation to phonocardiogra phy St Louis 1965 The C V Mosby Company pp 51 53
3. Fletcher H Speech and hearing New York 1929 D Van Nostrand Co Inc.
4. Tavel M E The fourth heart sound Circulation 49 1964 1974
5. Spodick D H On experts and expertise The effects of variability in observer performance Am J Cardiol 36 592 19 5

interobserver variability when experts in many fields including auscultators have had to report on exactly what they perceived in the absence of other information.[5] In these investigations and strikingly among expert auscultators given quite simple auscultatory challenges the acoustic information was identical but its perception and its interpretation were surprisingly different.[6]

Statement of the problem specific

Recent investigations of S_4 audibility and the occurrence at least of phonocardiographic S_4 in normal persons have included for the first time actual observer performance studies.[11] Outstanding authorities have written mature and reasoned challenges of the results [illegible] although from the outset it was admitted that this work is imperfect and raises more questions than it answers.[16] Yet the challenges stand on rather solid ground because phonocardiographic S_4 vibrations average about 20 Hz,[11] and classic audiometric studies[7] indicate that without unusual amplification this frequency will not be perceived as sound because of the logarithmic response of the human auditory apparatus. Moreover traditional auscultatory doctrine holds that the thresholds of S_4 perception and of pathologic significance are approximately the same. This is a fortunate coincidence which while not rigorously proved, is not entirely implausible because there is no disagreement on high intensity and palpable fourth heart sounds.

The questions of audible S_4 and the significance of phonocardiographic S_4 in ostensibly normal persons arose from a combination of both agreed and controversial clinical and laboratory observations. These may be summarized as follows:

1 All persons with contracting atria and without greatly shortened P R intervals have a potential S_4 which is essentially a concurrent but higher frequency correlate of the same presystolic events that produce the precordial A wave.

2 Phonocardiographic registration of definite and often relatively large S_4s is quite common in normal persons particularly after age 40 in whom the prevalence of S_4 by PCG may approach or equal its prevalence in patients with diseases reducing ventricular compliance.[13,17]

3 Phonocardiography can time an event with some precision but recordability is not tantamount to audibility particularly for lower frequency vibrations. Yet phonocardiography is the practical standard for heart sound registration and auscultatory performance.

4 Audiometric responses to artificially generated pure tones at various frequency-amplitude products may not be equivalent to auscultatory performance with complex biologic sounds in the presence of overtones and mixed frequency spectra. Yet audiometry is the theoretic standard for audibility.

5 S_4 may be present when a binary acoustic event associated with S_1 occurs in the sequence low pitched sound preceding high pitched sound, i e its components are perceived by auscultation as "dull - sharp."

Number 5 is the crux of the problem at the bedside. There is no disagreement about the crisp split components of the second heart sound which is both physiologically and clinically a much less complex and better understood phenomenon than S_1. Yet both the components of the S_1 split should be—and often are— sharp to the ear in normal individuals and in patients without severe valvular or myocardial damage. Thus in such individuals an S_1 split should be perceived as a pair of different but rather high pitched sounds, i e its components are perceived by auscultation as sharp - sharp. In contrast, one or both S_1 split components may become attenuated or dull under conditions such as acute myocardial infarction severe myocardial disease A V valve regurgitation shock left bundle branch block or A V conduction delay. Many such patients of course have an undisputed pathologic S_4 and are not the subject of debate.

The question of S_4 audibility arises in those individuals normal and diseased in whom the major components of S_1 ought to be (clinically at least) at their customary high pitch and indeed on the PCG appear to register as high frequency oscillations.[illegible] If under these circumstances auscultators perceive a binary acoustic event in the sequence dull - sharp they usually have but two choices either $S_4 + S_1$ or attenuated S_1, i e auscultatory dulling of its first component. They may choose the former if they think the events too widely separated to be S_1 components but this may be highly subjective. Moreover similar relative timing could equally apply to yet another but less likely combination attenuated S + click. Here it should be mentioned that in practice proper form in examining the heart requires doing two things at once

Clinical communications

Programmed left ventricular contrast injection

A METHOD TO MINIMIZE LEFT VENTRICULAR IRRITABILITY DURING ANGIOGRAPHY

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Since the advent of left ventricular angiography in the 1950s arrhythmias occurring with the power injection of radiographic contrast material have been a continuing problem Most frequently the arrhythmia consists of one or more premature ventricular contractions (PVC s) which often result in a nondiagnostic ventriculogram Less frequently premature atrial contractions (PAC s) ventricular tachycardia or fibrillation may occur Little has been written on the incidence of arrhythmias with left ventricular (LV) angiography nor has a systematic approach been formulated to reduce their occurrence

This study defines the frequency of arrhythmias during LV angiography and relates their occurrence to catheter design ventricular size and to the timing of onset of the injection relative to the cardiac cycle Efforts to minimize ventricular irritability by controlling the rate of pressure development and by limiting the onset of injection to late diastole are described

Methods

A total of 372 consecutive records of LV angiograms were examined from the strip chart recording of the electrocardiogram (ECG) injection marker and filming indicator to obtain 300 in which all of this information was available Seventy two record were excluded because either the onset of injection or the filming marker had not been recorded All these LV contrast injections were performed with a Cordis Model II pressure injector using warm (37° C) meglumine diatrizoate sodium (Hypaque 75 M Winthrop) Prior to injection every effort was made to find a position in the left ventricle where a vigorous 10 c c hand injection of contrast material did not produce PVC s Generally this quiet area was with the catheter tip directed posteriorly and medially toward the mitral valve From these records and the catheterization reports the following information was recorded (1) the interval in seconds from the peak of the R wave of the QRS to the onset of injection (R I) (2) duration in seconds of the cardiac cycle within which onset of injection occurred (R R) (3) arrhythmia initiated by the injection (4) arrhythmia present prior to injection (5) type of catheter used (6) contrast volume used (7) injection pressure used (8) LV end diastolic volume per square meter (EDV/M) end systolic volume (ESV/M ²) and LV ejection fraction ([EDV ESV EDV] × 100) as determined by the area length method of Dodge and associates

To adjust for variation in heart rate the R I was expressed as a per cent of the R R (R I/ R R × 100)

Two hundred twenty two consecutive LV angiograms were performed with a Viamonte Hobbs Angiomat 3000 injector A 40 to 60 ml quantity of contrast material (Hypaque 75M) was injected at 20 ml per second The onset of injection was controlled relative to the cardiac cycle with the ECG triggering device On alternate injections an 0 6 second delay in the development of peak pressure was used to reduce catheter whip

Statistical analysis of the frequency and distri

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6. Caceres C and Perry L The innocent murmur Boston 1967 Little Brown & Company
7. Rectra E H Khan A H Pigott V M and Spodick D H Audibility of the fourth heart sound A prospective blind auscultatory and polygraphic investigation J A M A **221** 36 1972
8. Spodick D H and Quarry Pigott V M The fourth heart sound Normal findings in older persons N Engl J Med **288** 140 1973
9. Spodick D H and Quarry V M Prevalence of the fourth heart sound by phonocardiography in the absence of cardiac disease AM HEART J **87** 11 1974
10. Swistak M Mushlin H and Spodick D H Comparative prevalence of the fourth heart sound in hypertensive and matched normal persons Am J Cardiol **33** 614 1974
11. Kino M Shahamatpour A and Spodick D H Auscultatory perception of S The effects of S-S interval and aging Am J Cardiol **37** 848 1976
12. Tavel M E The fourth heart sound—A premature requiem? Circulation **49** 4 1974
13. Wayne H Significance of the fourth heart sound AM HEART J **88** 126 1974
14. Fowler N O and Adolph R J Fourth sound gallop or split first sound? Am J Cardiol **30** 441 19[illegible]
15. Abrams J The fourth heart sound—A normal finding Am J Cardiol **36** 534 197[illegible]
16. Spodick D H The fourth heart sound An inadequately investigated subject Am J Cardiol **36** [illegible] 19[illegible]
17. Tavel M E Kavalier M A and Stewart J The apical A wave versus the fourth heart sound in aortic stenosis (Abstr) Circulation **49**(III) 247 1974
18. Bethell H J N and Nixon P G F Understanding the atrial sound Br Heart J **35** 229 1973
19. Prakash R Aytan N Dhingra R Chhablani R and Rosen K M Variability in the detection of a fourth heart sound—Its clinical significance in elderly subjects Cardiology **59** 49 1974
20. Singh R Grampton R S and Horgan J A Physical electrocardiographic and hemodynamic features of the athletic heart syndrome Clin Res **23** 8A 197[illegible]
21. Spodick D H Kino M Huggins A W F and Pickett R (Unpublished observations)

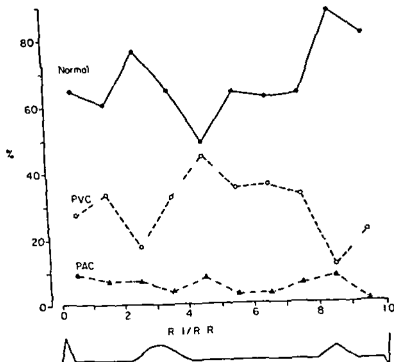


Fig 2 Per cent of contrast injections starting during each 10 per cent of the cardiac cycle which were associated with beats with only normal QRS configuration which induced one or more PVC s or which induced one or more PAC s

the T wave were associated with the highest frequency of PVC s reaching more than 40 per cent during the 0 4 to 0 5 interval

Five different catheter types in Fr sizes either 7 or 8 were used for the 300 injections The catheter type number of injections and frequency of injection induced arrhythmias are shown in Table II and in Fig 3 The Gensini catheter was used 66 per cent of the time and with 24 per cent of these injections PVC s occurred Injections through a pigtail catheter produced PVC s more than one third of the time PVC s were also frequent with the use of other catheters The difference in the incidence of injection induced PVC s between Gensini and pigtail catheters was statistically significant ($p < 0\ 05$)

The relationship between the volume of contrast agent used and frequency of arrhythmias was evaluated Within the range of 40 to 80 ml of contrast agent used in these examinations the volume had no influence on the production of PVC s or PAC s

End-diastolic ventricular volume defined as normal (< 100 ml per square meter) and

Table II Retrospective

Type of catheter	Frequency of use		Frequency of PVC s		Frequency of PAC s	
	No	%	No	%	No	%
Pigtail	8.	29	31	3	6	7
Gensini	196	66	48	24 5	10	5
Brockenbrough	4	1	2	50	0	
Eppendorf	7	2	2	28	1	4
Millar	6	2	0		0	
Sones	2	0 7	0		0	
Total	300		83		17	

enlarged (> 100 ml per square meter) was evaluated for its influence on the frequency of injection induced arrhythmias (Fig 4) There was a lower frequency of PVC s (18 per cent) when contrast was injected into an enlarged chamber as compared to one of normal volume (28 per cent) but this difference did not reach statistical signif

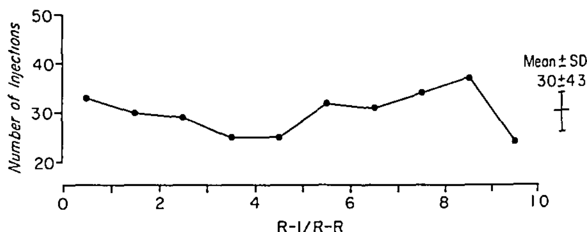


Fig 1 Number of contrast injections which had their onset during each 10 per cent of the cardiac cycle in 300 LV angiograms

Table I Distribution of onset of injection

	R I/R R interval											
	0 0 0 10	*0 11 0 20*	*0 21 0 30*	*0 31 0 40*	*0 41 0 50*	*0 51 0 60*	*0 61 0 70*	*0 71 0 80*	*0 81 0 90*	*0 91 1 0*	*Total*	*Mean ± SD*
A Retrospective												
No of injections	33	30	29	25	25	32	31	34	37	24	300	30 ± 4 3
No with PVC s	9 (27)*	10 (33)	5 (17)	8 (32)	11 (44)	11 (34)	11 (35)	11 (32)	4 (11)	5 (21)	85 (28)	8 5 ± 2 8
No with PAC s	3 (9)	2 (7)	2 (7)	1 (4)	2 (8)	1 (3)	1 (3)	2 (6)	3 (8)	0 (0)	17 (6)	1 7 ± 0 95
B Prospective												
No of injections			50†			88†			84†		222	
No with PVC s			18 (36)			22 (25)			27 (32)		67 (30)	
No with PAC s			1 (2)			3 (3)			1 (1)		5 (2)	

Number in parentheses indicates per cent of all injections in that interval
†Number represents total for intervals 0 0 to 50 51 to 0 and 71 to 1 0 respectively

bution of arrhythmias occurring during injection beginning in various intervals of the cardiac cycle was by the 2 × K contingency test

Results

Retrospective study The distribution of onset of injection for each portion of the cardiac cycle is shown in Fig 1 The distribution is relatively even with the number of injections in each 10 percentile being within 2 S D of the mean (30 ± 4 3) The frequency of use of the various catheter types for each 10 percentile of the cardiac cycle was analyzed in a similar manner There was no significant difference in the distribution of use

The relationship between the time of onset of injection and the occurrence of injection induced arrhythmias was analyzed for each 10 per cent period of the cardiac cycle The data are displayed in Fig 2 and Table I A The frequency of PAC s was 6 per cent and unrelated to the time of injection PVC s occurred in 28 per cent of injections and were statistically more frequent when the injection occurred during the first 70 per cent of the R R interval ($p < 0\ 03$) Injection without associated arrhythmia occurred most frequently when the injection began during the interval between 0 8 and 0 9 of the cardiac cycle which usually corresponds to the P wave of the ECG Injections which began during the downslope of

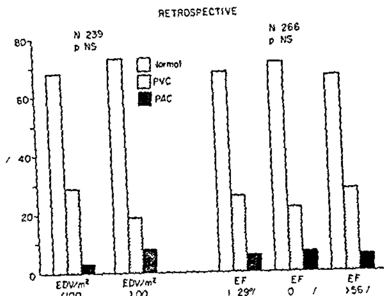


Fig 4 Per cent of contrast injections into left ventricles with normal or enlarged end-diastolic volumes and with normal moderately depressed or severely depressed ejection fractions which induced one or more PVCs or PACs

tions and to develop methods which reduce the frequency of their occurrence

Because of this laboratory's long time interest in quantitative angiography special attention has been directed toward the avoidance of injection induced PVCs The catheter tip has usually been placed in a posterior medial direction so that contrast material is directed against the mitral valve This catheter position has resulted in a less than 2 per cent incidence of PVCs prior to the onset of injection and in these few patients spontaneous PVCs were present prior to LV catheterization Despite attention to these details power injection produced PVCs have been very frequent occurring in 28 per cent of all LV injections

It is likely that most injection induced PVCs result from the catheter impinging on the LV endocardium as the catheter straightens (whips) with the rapid rise in luminal pressure This whipping motion is readily appreciated on LV cineangiograms Injection into the enlarging late diastolic chamber should therefore reduce the opportunity for the catheter to strike the endocardium Our observation of few PVCs occurring with injections initiated in late diastole support this thesis

It is well known that the ventricular myocardium is most susceptible to stimulation during the so called hyperexcitable period This corresponds to the short interval beginning during the terminal portion of the T wave and coincides with end systole The initiation of pressure injection during this period (0 4 to 0 5) was associated with the highest frequency of PVCs (44 per cent) We are uncertain as to which has the greater influence—the small ventricular size or increased myocardial excitability present during this portion of the cardiac cycle

The higher incidence of injection stimulated PVCs with the pigtail catheter as compared to the relatively straight Gensini catheter suggests that the loop configuration increases the likelihood of mechanical and endocardial stimulation

Because of these considerations onset of injection was limited to the last 50 per cent of the cardiac cycle (172 injections) The rate of development of injection pressure was limited in order to reduce catheter whip (91 injections) The over all frequency of development of PVCs was 28 per cent—the same as for the retrospective study—and was not altered by the use of pressure rate rise limitation In comparing the Gensini and the pigtail catheter the difference in frequency of PVCs was highly significant (18 per cent and 47 per cent respectively) However this difference was also present in the retrospective studies for

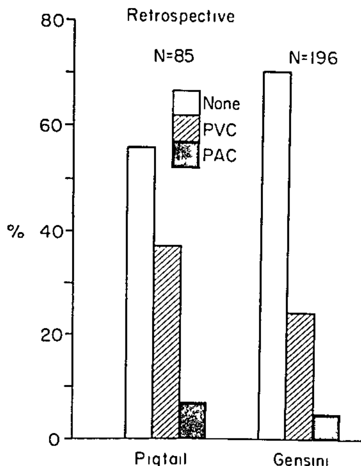


Fig 3 Per cent of LV contrast injections using either a pigtail or Gensini catheter which induced one or more PVC s or PAC s

icance When similar analysis was done on patients with a low ejection fraction (EF) (< 29 per cent), moderately reduced EF (30 to 55 per cent) and normal EF (> 56 per cent) there was no difference in the frequency of PVC s (Fig 4) There was no significant difference in distribution of patients with a low EF in each 10 percentile of the cardiac cycle The same was true for those with moderately reduced and normal EF as well as those with normal and enlarged EDV per square meter

The pressures used for LV contrast injection ranged from 250 to 500 p s i No correlation existed between pressure used and occurrence of arrhythmia

Prospective study For various technical reasons 50 of the 222 prospective ECG controlled injections occurred in the initial one half of the cardiac cycle No further analysis is made of these One hundred seventy two injections in the terminal 50 per cent of the cardiac cycle induced PVC s in 29 (28 per cent) and PAC s in 3 (3 per cent) This was the same as for the 300 retrospective injections The frequency of PVC s during the terminal 30 per cent of the cycle was also similar (32 per cent) and not statistically different from the same period of the retrospective study (Table I)

Pressure rate rise delay was used in 91 injections during the last 50 per cent of the cycle and no delay in 81 PVC s were induced in 24 (20 per cent) in the former and in 25 (31 per cent) in the latter (p = N S) The number of injections and frequency of PVC s were similar for the interval 51 to 70 and 71 to 1 0 and were unaffected by the use of rate rise delay

The pigtail catheter was used for 62 injection in the terminal half of the cycle and PVC s occurred in 29 of these (47 per cent) The Gensini catheter was used for 108 injections during the same interval with PVC s occurring at a frequency of 18 per cent Difference between the pigtail and the Gensini is highly significant ($p < 0.001$) The use of pressure rate rise delay did not alter the incidence of PVC s for either catheter

As with retrospective cases there was no relationship between normal or enlarged end diastolic volumes and injection induced arrhythmias or between high and low ejection fractions and arrhythmias

Discussion

Life threatening arrhythmias including ventricular fibrillation ventricular asystole and prolonged ventricular tachycardia are recognized but infrequent complications of left ventricular angiography In the prospective Cooperative Study on Cardiac Catheterization which included 5212 LV angiograms ventricular fibrillation occurred in two (0 04 per cent) sustained ventricular tachycardia requiring countershock or other treatment occurred in two (0 04 per cent) and severe bradycardia or asystole in one (0 02 per cent) [1] In our small series there were no episodes of ventricular fibrillation sustained ventricular tachycardia or asystole Ventricular tachycardia defined as three or more consecutive ventricular beats occurred with 11 of 300 injections (3 7 per cent) and all spontaneously converted to normal at the end of the contrast injection

This study was designed to determine the frequency of contrast injection induced ventricular and supraventricular premature contrac

Left ventricular contractile function in aortic stenosis evaluated by isovolumic and ejection phase indexes

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Whereas the severity of valvular lesions is readily assessed by standard hemodynamic and cineangiographic measurements the quantitation of the contractile state of the myocardium remains a major challenge for the cardiologist Although numerous indexes derived either from isovolumic left ventricular pressure measurements[1] or from changes of the left ventricular cineangiographic silhouette during the ejection period[7] have been proposed for the evaluation of the contractile tate there is at the present time no single index that is valid under all hemodynamic conditions From recent investigations it appears that the reliability of the different parameters can vary considerably according to the clinical setting In patients with diffuse myocardial disease ejection phase contractile indexes were found to be preferable to the isovolumic indexes for the detection of abnormal contractile function in the basal state On the other hand total pressure isovolumic indexes were significantly diminished in a group of pediatric patients with a chronic pressure overload of the left ventricle in whom the ejection performance as evaluated by the systolic ejection fraction was normal In view of these discrepancies the present study was undertaken to reappraise the value of isovolumic as well as ejection phase indexes for detecting abnormal left ventricular function in adults with a specific clinical setting such as aortic stenosis

Methods

Patients Forty one patients with pure or predominant aortic stenosis were studied for diagnostic purposes by right and left heart catheterization and cineangiography Premedication consisted of 10 mg of Librium given orally 1 hour before catheterization Twelve patients were receiving digitalis at the time of study Following the diagnostic part of the catheterization a micromanometer catheter (Statham SF 1 or Millar) was inserted transseptally into the left ventricle[1] Aortic pressure was measured either by the conventional technique or by a tipmanometer catheter introduced through a femoral artery Cardiac output was determined by thermodilution Small to moderate aortic regurgitation as assessed by thermodilution and/or by cineangiography was present in 24 patients Evaluation of combined aortic mitral regurgitation by thermodilution in two patients and by left ventricular cineangiography in one revealed a slight mitral incompetence In one patient a small ventricular septal defect was present Selective coronary arteriography was carried out at the end of the investigation in 28 of the 41 patients In one patient (No 21) a 70 per cent stenosis of the left circumflex artery was detected There were however no signs of localized wall motion abnormalities at left ventricular cineangiography All patients were in sinus rhythm and the duration of the QRS did not exceed 0 11 sec

Isovolumic contractile indexes From the left

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injections during the terminal half of the cardiac cycle Moreover this incidence of PVC s with the Gensini in the prospective study was not statistically different from the incidence of PVC s with the Gensini catheter for any interval during the retrospective study

The use of pressure rate rise delay and ECG triggering of the left ventricular power injections adds little towards reducing the risk of the left ventricular angiography or increasing the diagnostic yield when using the pigtail or Gensini catheters

Summary

Left ventricular angiography frequently produces one or more premature atrial or ventricular contractions which may make quantitative volume analysis unreliable Three hundred left ventricular power injections were analyzed and found to produce premature ventricular contractions (PVC s) in 28 per cent of injections and PAC s in 6 per cent Forty four per cent of injections starting near the end of the T wave were associated with PVC s whereas those starting near the end of diastole during the P wave produced PVC s in only 11 per cent Injection through a Gensini catheter were associated with PVC s in 24 per cent compared to 37 per cent when a pigtail catheter was used ($p < 0.05$)

The introduction of an 0 6 second delay in the development of peak injection pressures and ECG triggering to start the injection in the last half of the cardiac cycle did not alter the incidence of PVC s The use of timed diastolic injections with pressure rate rise delay is of little value in reducing injection induced arrhythmias

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REFERENCES

1 McIntosh H D Arrhythmias Cooperative study cardiac catheterization Circulation **37 38**(Suppl III) 27 1968
2 Mandel D Angiocardiography *in* A practice of cardiac catheterization Edinburgh 1974 Blackwell Scientific Publications chap 16 pp 351 358
3 Dodge H T Sandler H Ballew D W and Herd J The use of biplane angiocardiography for the measurement of left ventricular volume in man AM HEART **60** 762 1960

Table I Normal ranges in our laboratory for cineangiographic data*

Parameter	Mean	Range	Remarks
EDVI (ml/M)	86	59–121	Obtained from a group of 34 subjects (2? ♂ 12 ♀) that comprised 28 subjects without cardiac disease and 6 patients with uncomplicated atrial septal defect
ESVI (ml/M)	26	16–35	
EF	0 70	0 6?–0 78	
mean V (circ/sec)	1 43	1 00–1 92	
MNSER (EDVs/sec)	2 46	2 00–3 ?4	
HR (beats/min)	79	42–120	
Age (yr)	40	18–63	
Wall thickness (cm)	0 79	0 53–1 04	Obtained from a group of 19 subjects (11 ♂ 8 ♀) that comprised 8 subjects without cardiac disease and 11 patients with uncomplicated atrial septal defect or anomalous pulmonary venous drainage *Unpublished observations*
LMMI (Gm/M)	87	50–129	
EDVI (ml/M)	88	59–115	
HR (beats/min)	79	56–104	
Age (yr)	3?	19–60	

*Abbreviations EDVI left ventricular end-diastolic volume index ESVI left ventricular end-systolic volume index EF *ejection fraction mean* V_{cf} mean velocity of circumferential fiber shortening MNSER mean normalized systolic ejection rate HR, heart rate LMMI left ventricular muscle mass index

filming sequence prior to the heart beat that was analyzed quantitatively The end diastolic volume (EDV) and the end systolic volume (ESV) were determined by the area length technique [6] whereby the long ventricular axis was drawn individually in both silhouettes from the mitral aortic juncture to the apex Ejection fraction (EF) was calculated as (EDV ESV)/EDV From the same RAO end diastolic and end systolic silhouettes the mean velocity of circumferential fiber shortening was calculated according to the formula

$$\text{mean } V_{cf} \text{ (in circumferences/sec)} = \frac{(M_D - M_s)}{ET \; M_D}$$

whereby

M_D = minor axis of the left ventricular end diastolic silhouette measured at the midpoint of the long axis

M_s = minor axis of the left ventricular end systolic silhouette measured at the midpoint of the long axis

ET = ejection time determined from the aortic pressure curve (in the four patients with slight mitral incompetence or ventricular septal defect 0 05 sec was added to the measured ejection time)

Mean normalized systolic ejection rate was calculated as EF/ET in end diastolic volumes/sec

For the normal ranges of the volumetric parameters and of the ejection phase contractile indexes valid for our laboratory [17] see Table I

Left ventricular wall thickness and mass In 39 of the 41 patients an additional cineventriculogram was carried out in the A P projection for determining the thickness of the free left ventricular wall [9] In two patients (Nos 27 and 31) the thickness was measured in the middle third of the anterior contour of the RAO cineventriculogram By adding the end-diastolic wall thickness corrected for x ray magnification to the ends of the calculated minor axis and of the measured long axis of the RAO silhouette both corrected for magnification total left ventricular volume (TLVV) was then calculated Left ventricular muscle mass (LMM) was obtained from the formula

$$LMM = (TLVV - EDV) \; 1 05$$

where 1 05 = specific density of heart muscle [16] Our normal ranges for wall thickness and left ventricular muscle mass are listed in Table I

Results

Contractile indexes and definition of patient groups Table II shows the isovolumic contractile indexes as well as the data derived from left ventricular cineangiograms In patients Nos 1 to 17 both the isovolumic contractile indexes (Vmax and Vpm) and the ejection phase contractile indexes (mean V_{cf} and MNSER) were within the normal ranges established for our laboratory (Table I) These patients constitute Group 1 In the patients Nos 18 to 26 (Group 2) both the isovolumic and the ejection phase indexes were depressed except in patient No 21 who had only one of the ejection parameters below the normal

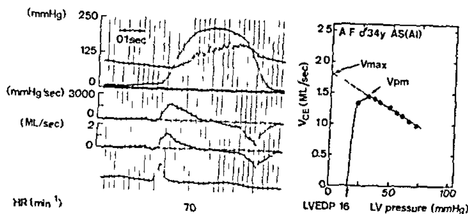


Fig 1 Left ventricular and aortic high fidelity pressure curves (on the left) and pressure velocity relation (on the right) in patient No 17 (Tables II and III) Vmax was obtained by manual linear extrapolation of the descending portion of the pressure velocity curve In the panel on the left are shown from top to bottom aortic pressure left ventricular pressure first derivative of left ventricular pressure (dP/dt) instantaneous velocity of shortening of the contractile elements (V) and FCG Abbreviations *HR* heart rate *LVEDP* left ventricular end diastolic pressure *Vpm* peak measured velocity of shortening of the contractile elements

ventricular high fidelity pressure curve (Fig 1) the first derivative (dP/dt) and the instantaneous quotient (dP/dt)/P were obtained by an analogue computer[11] The velocity of shortening of the contractile elements (V_{CE}) during the isovolumic phase of left ventricular systole was determined according to the formula

$$V_{CE} \text{ in muscle lengths (ML)/sec} = (dP/dt)/28\ P$$

where P represents intraventricular pressure and 28 the coefficient of series elasticity *[11] Zero reference was set at the midthoracic level determined in the fourth intercostal space

The two total pressure contractile indexes used in this study were Vmax and peak measured isovolumic velocity of shortening (Vpm) Vmax was obtained by manual linear extrapolation of the descending limb of the pressure velocity curves (Fig 1) As shown previously there is an excellent agreement between the manually determined Vmax and the mathematically (least squared fit) calculated Vmax The normal range in our laboratory for Vmax is from 1 47 to 2 39 ML/sec and for Vpm from 1 14 to 1 96 ML/sec[14] These ranges are similar to those reported by Peterson and associates Developed pressure isovolumic indexes were not calculated since they have been shown to be completely unreliable for detecting a reduced contractility in patients with undebatably depressed left ventricular function at rest

Ejection phase contractile indexes The two ejection phase indexes we used in this study were mean velocity of circumferential fiber shortening (mean V_{CF}) and mean normalized systolic ejection rate (MNSER) since both indexes have been shown to be most useful for the detection of abnormal left ventricular function They were derived from cineventriculograms in the right anterior oblique (RAO) projection carried out after recording the high fidelity pressure curve The difference between the heart rate of the pressure run and that of the RAO cineangiogram exceeded 9 beats per minute in only four of the patients

Left ventricular cineangiography was performed at midinspiration at a filming rate of frames per second Contrast dye (Urografin 76 percent) was delivered by a power injector (Contrac Siemens) through the F11 Brockenbrough catheter in amounts varying between 25 and 40 ml At the end of the procedure a calibration grid with squares of 1 cm was filmed at the level of the center of gravity of the left ventricle This level was estimated from a chest roentgenogram in the left anterior oblique projection For the quantitative analysis the cinefilms were viewed at the Tage Arnø projector By playing back and forth the largest (= end diastolic) and the smallest (= end systolic) left ventricular silhouette was identified In the 41 cineventriculograms no extrasystoles were present during the entire

* The problems inherent to the assumption of an identical coefficient of series elasticity (K value) in all patients are recognized Although in cats myocardial hypertrophy from chronic pressure overload has been shown not to alter series elasticity it cannot be excluded that in the present clinical setting and especially in the patients with additional aortic insufficiency hypertrophy was sometimes associated with fibrosis which would tend to reduce the K value Thus scatter in isovolumic contractile indexes may reflect in part probable inconstancy of the series elastic properties

Table II cont d

Case No	BSA (M)	Vpm (ML /sec)	Vmax (ML /sec)	EDVI (ml /M)	HR (beats/ min)	EF	mean V (circ /sec)	MNSER (EDVs/ sec)	h (cm)	LMMI (Gm /M)
Group 3 (ejection phase indexes normal isovolumic indexes depressed)										
27	1 61	1 02	1.39	96	65	0 67	1 4?	? 28	1 19	157
28	1 84	0 96	1 31	73	81	0 60	1 08	2.08	1 71	208
29	1 75	1 12	1 23	7?	74	0 79	1 45	2 29	1 21	137
30	1 72	1 05	1 55	173	78	0 82	1 42	2 48	1 35	249
31	1 ,0	1 30	1.37	81	60	0 67	1 36	2.06	1 45	190
32	1 73	1 03	1 18	105	66	0 80	1 59	2 48	1 16	154
33	1 83	0 96	1 29	66	58	0 75	1 27	2 54	1 46	160
34	1 81	1 19	1 42	,9	64	0 77	1.36	2.38	1 30	152
35	1.58	0 79	0 91	134	61	0 76	1.31	2.07	1 16	164
Mean	1 73	1 05	1 29	97	67	0 74	1 36	2.30	1 33	177
± 1 S D	0 09	0 15	0 18	35	8	0 07	0 14	0 19	0 18	35
P vs Gr 1	NS	< 0 001	< 0 001	NS	NS	NS	NS	NS	< 0 05	NS
P vs Gr 2	NS	< 0 05	NS	< 0 0,	NS	< 0 001	< 0 001	< 0 001	NS	NS
Group 4 (isovolumic indexes normal ejection phase indexes depressed)										
36	1 33	1 17	1 62	70	7?	0 62	0 89	1.99	1.22	152
37	1 90	1.20	1.53	75	61	0 69	0 77	1 87	0 82	78
38	1 79	1.36	2.06	90	70	0 54	0 89	1 58	1 07	126
39	1 66	1 50	2 14	95	70	0 6?	0 89	2 02	0 99	120
40	2.1?	1 29	1 66	94	73	0 65	1 14	1 90	1.55	193
41	1 75	1 18	1 65	99	66	0 57	1 10	1 78	1.38	186
Mean	1 76	1 28	1 78	87	69	0 62	0 95	1 86	1 17	142
± 1 S D	0 26	0 13	0 26	12	4	0 0.	0 14	0 16	0 27	44
P vs. Gr 1	NS	NS	NS	NS	NS	< 0 01	< 0 001	< 0 001	NS	NS
P vs. Gr 2	NS	< 0 001	< 0 001	< 0 0?	NS	NS	NS	< 0 05	NS	< 0 05
P vs Gr 3	NS	< 0 01	< 0 001	NS	NS	< 0 01	< 0 001	< 0 002	NS	NS

When the isovolumic and the ejection phase parameters were combined for disclosing a depressed left ventricular function 24 patients (59 per cent) were found to have at least one of the four contractile indexes below the range of normality

Conventional hemodynamics The four groups as defined above were then analyzed separately with respect to a possible influence of other variables Age body surface area left ventricular peak systolic pressure heart rate during pressure recording and cineangiography mean systolic pressure gradient between the left ventricle and the ascending aorta and the systolic aortic valve area were not significantly different in the four groups (Table III) Left ventricular end diastolic pressure was significantly increased in Groups 2 to 4 (28 21 and 20 mm Hg respectively P values < 0 001 < 0 01 and < 0 0.) as compared to Group 1 (14 mm Hg) Between Groups 3 and 4 with discordant isovolumic and ejection phase indexes there was no difference in left ventricular end diastolic pressure Cardiac index was significantly decrea ed in Groups 2 (2 5 L /min M ²) and 3 (2 6 L /min M ²) as compared to Group 1 (3 7 L /min M ²) Although cardiac index was higher in Group 4 (3 3 L /min M ²) than in Group 3 the difference was not significant End diastolic volume/M ² (EDVI) was significantly increased in Group 2 (144 ml /M ² P < 0 001) as compared to Group 1 (89 ml /M ²) Between the EDVI in Group 3 (97 ml /M ²) and in Group 4 (87 ml /M ²) there was no significant difference End diastolic wall thickness was largest in Group 3 (1.33 cm) and was significantly (P < 0 05) increased when compared with Group 1 Between Group 3 and Group 4 there was no significant difference in wall thickness Left ventricular muscle mass/M ² (LMMI) was significantly (P < 0 01) higher in Group 2 (200 Gm /M ²) than in Group 1 (140 Gm /M ²) In Group 3 LMMI was higher (177 Gm/M ²) than in Group 4 (142 Gm/ M ²) although the difference did not reach a significant P value

Table II Isovolumic contractile indexes and angiographic data*

Case No	BSA (M^2)	Vpm (ML/sec)	Vmax (ML/sec)	EDVI (ml/M^2)	HR (beats/min)	EF	mean V_{cf} (circ/sec)	MNSER (EDVs/sec)	h (cm)	LMMI (Gm./M)
Group 1 (both isovolumic and ejection phase indexes normal)										
1	1 48	1 54	1 87	87	82	0 72	1 37	2 37	0 96	117
2	1 77	1 34	1 47	87	71	0 76	1 13	2 61	1 29	161
3	1 62	1 61	2 02	88	95	0 66	1 20	2 48	1 07	126
4	1 72	1 38	1 74	97	69	0 60	1 24	2.22	0 98	117
5	1 50	1 58	1 95	121	90	0 64	1 21	2 00	1 36	223
6	1 68	1 41	1 91	104	75	0 66	1 36	2 20	1 40	195
7	1 72	1 34	1 76	74	67	0 81	1 93	2 68	0 86	8[illegible]
8	1 79	2 00	2 52	92	99	0 75	1 45	2.75	0 90	100
9	1 74	1 37	2 00	85	74	0 84	1 98	2 90	1 24	157
10	1 56	1 82	2 26	59	84	0 79	1 63	2 48	0 85	79
11	1 74	1 29	1 77	106	61	0 86	2 18	3 07	1 08	139
12	1 72	1 27	1 79	77	57	0 74	1 26	2 30	0 86	89
13	2 26	1 32	1 86	113	68	0 85	1 76	2 53	1 43	190
14	1 65	1 21	1 57	113	67	0 82	1 31	2 34	1 68	[illegible]
15	1 78	1 34	1 80	78	72	0 68	1 80	2.31	1 25	141
16	1 77	1 59	2 14	38	72	0 71	1 88	2 25	1 2[illegible]	94
17	1 87	1 31	2 01	90	68	0 73	1 56	2 25	0 90	99
Mean	1 73	1 45	1 91	89	75	0 74	1 54	2 46	1 14	140
± 1 S D	0 17	0 21	0 25	21	12	0 08	0 32	0 28	0 24	54
Group 2 (both isovolumic and ejection phase indexes depressed)										
18	1 98	1 11	1 42	88	90	0 58	0 69	1 69	1 46	180
19	1 64	0 80	1 04	110	94	0 44	0 57	1 33	1 29	193
20	2 02	1 00	1 09	92	85	0 47	0 62	1 55	1 35	169
21	1 74	0 80	1 20	128	56	0 56	1 68	1 65	1 19	174
22	1 67	1 09	1 30	127	74	0 33	0 54	1 02	1 04	150
23	1 63	0 80	1 09	169	69	0 70	0 94	1 96	1 32	248
24	1 77	0 82	1 26	204	58	0 53	0 85	1 66	1 35	273
25	1 78	0 54	0 75	178	78	0 37	0 45	1 26	1 20	210
26	1 96	0 73	1 15	204	68	0 66	0 96	1 81	1 16	213
Mean	1 80	0 85	1 14	144	75	0 52	0 81	1 55	1 26	200
± 1 S D	0 15	0 18	0 19	45	13	0 12	0 37	0 29	0 13	40
P vs Gr 1	NS	< 0 001	< 0 001	< 0 001	NS	< 0 001	< 0 001	< 0 001	NS	< 0 01

Abbreviations BSA body surface area Vpm peak measured velocity of shortening of the contractile elements Vmax maximal extrapolated velocity of shortening of the contractile elements EDVI left ventricular end diastolic volume index HR heart rate during cineangiography EF ejection fraction mean V_{cf} mean velocity of circumferential fiber shortening MNSER mean normalized systolic ejection rate h end diastolic wall thickness LMMI left ventricular muscle mass index S D standard deviation Gr group P probability (unpaired t test) NS not significant (P > 0 05)

range It is noteworthy that in Group 2 a significant aortic insufficiency (fao > 0 30 Table III) was present in five out of nine patients (56 per cent), representing the highest score of an associated regurgitant lesion in all four groups Thus the combination of a chronic pressure overload with an additional volume overload appears to be particularly effective in inducing myocardial depression as judged from the reduction of both the isovolumic and the ejection phase parameters In patients 27 to 41 the isovolumic and the ejection phase indexes were discordant In the cases 27 to 35 the ejection phase indexes were normal and Vmax and/or Vpm were depressed (Group 3) The last six cases (no 36 to 41) had normal isovolumic indexes and mean V_{cf} and/or MNSER was diminished (Group 4) In Figs 2 to 5 the patients of Group 1 are located in the upper right quadrant those of Group 2 in the lower left quadrant those of Group 3 in the upper left, and those of Group 4 in the lower right quadrant In summary an abnormal left ventricular contractile function was detected based on Vmax in 17 of 41 patients (42 per cent) on Vpm in 16 patients (39 per cent) on mean V_{cf} in 12 (29 per cent), and based on MNSER in 14 patients (34 per cent)

AVA (cm²)	Diagnosis	Comments
0 5	AS	digital †
0 65	AS AI	fao 0 06
1 4	AS cong	
0 7	AS	†
0 3	AS	†
1 0	AS	†
0 6	AS	†
1 5	AS cong	
1 1	AS AI	fao 0 18
0 75	AS cong	
1 6	AS AI	fao 0 28†
0	AS	†
0 9	AS AI	fao 0 22†
0 8	AS AI VSD	fao 0 11 † L-R shunt 26%
0 8	AS	†
0 6	AS	digital †
1 2	AS AI	fao 0 09†
0.88		
0 38		
0 9	AS AI	fao 0 50†
0 45	AS AI MI	fao 0 50† digital
0 5	AS AI	fao 0 30† digital
0 4	AS CAD	sten LCx 70%†
0 7	AS AI	fao 0 33† digital
0 5	AS AI	fao 0 17 digital
0 8	AS AI	fao 0 28
1 0	AS AI MI	fao 0 41†
1 0	AS AI	fao 0 46† digital
0 69		
0 24		
NS		

ating left ventricular contractile function have yielded conflicting results In patients with compensated and decompensated left ventricular volume overload pressure overload or cardiomyopathy total pressure Vmax was found to be the most sensitive indicator of myocardial performance and showed a more consistent relationship to clinical congestive failure than the ejection fraction Similar conclusions with respect to sensitivity of indicating depressed left ventricular function can be drawn from the work of Graham and associates[3] because these authors reported a significantly reduced total pressure Vmax in a group of pediatric patients with a chronic pressure overload of the left ventricle in whom the ejection fraction was within the normal range In other series of pediatric patients with various forms of left ventricular disease total pressure Vmax[20] and peak measured velocity of the contractile elements[4] were generally depressed when abnormal left ventricular dynamics based on a decreased ejection fraction an increased end diastolic volume or increased end diastolic pressure were present In individual patients there was however overlap between the group considered to have normal cardiac function and that with abnormal conventional left ventricular dynamics Using the same criteria in addition to a normal cardiac index and absence of asynergy for defining normal left ventricular function Peterson and associates found that mean velocity of circumferential fiber shortening and mean normalized systolic ejection rate separated almost completely the subjects of a control group of normal persons from those of an abnormal group comprising patients with diffuse myocardial involvement In contrast to mean velocity of circumferential fiber shortening and mean normalized systolic ejection rate total pressure Vmax and peak measured isovolumic velocity of shortening showed some overlap between the patients in the normal and the abnormal group Thus the authors concluded that the ejection phase contractile indexes appear to offer a preferable mode for assessing myocardial function in the basal state Similarly Kreulen and associates[21] reported the isovolumic contractile indexes Vce 10 and Vmax calculated with developed pressure to be significantly less sensitive than ejection fraction end diastolic pressure or the presence of asynergy in detecting left ventricular dysfunction in patients with various forms of congenital valvular myocardial and coronary artery diseases These findings are not surprising since developed pressure contractile indexes have been previously demonstrated to be considerably less sensitive than total pressure indexes for detecting abnormal left ventricular function[9, 15] In the present study that was carried out in a series of patients with one predominant abnormal hemodynamic feature i e chronic pressure overload from aortic stenosis neither the isovolumic nor the ejection phase contractile indexes proved to be clearly superior for identifying depressed left ventricular contractile function although slightly more patients were found to have reduced isovolumic than reduced ejection phase indexes The largest number of patients was however detected to have abnormal contractile function when the isovolumic and the ejection phase

Table III Hemodynamics in patients with aortic stenosis*

Case No	Sex	Age (yr)	LVSP (mm Hg)	LVEDP (mm Hg)	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	HR (beats/ min)	LVET (msec)	CI (L/ min M²)	MSPG (mm Hg)
Group 1 (both isovolumic and ejection phase indexes normal)											
1	F	69	256	11	105	61	80	83	304	3 5	96
2	M	33	242	17	116	80	95	86	291	3 8	104
3	M	29	165	10	110	88	98	80	266	5 8	42
4	M	56	181	19	122	70	95	67	270	3 [illegible]	53
5	F	63	313	22	162	78	114	86	320	3 1	171
6	M	58	172	9	114	62	85	66	300	4 [illegible]	54
7	M	59	169	13	117	70	88	64	302	2 9	48
8	M	19	149	8	128	89	106	82	273	4 4	[illegible]
9	M	20	155	11	104	77	87	75	290	3 5	38
10	M	17	189	12	104	81	93	90	318	4 3	61
11	M	49	142	12	124	75	98	54	280	2 5	26
12	M	58	178	19	115	68	88	53	322	2 9	61
13	M	58	192	12	91	50	69	62	336	3 1	[illegible]
14	F	37	218	25	135	80	103	73	350	3 9	62
15	M	49	175	9	115	72	90	72	295	2 8	56
16	M	48	252	19	105	67	78	71	315	4 2	11
17	M	34	217	16	160	76	114	70	325	4 7	62
Mean		44	198	14	119	73	93	73	303	3 7	66
± 1 S D		17	46	5	19	10	12	11	24	0 8	30
Group 2 (both isovolumic and ejection phase indexes depressed)											
18	M	39	198	22	92	49	67	59	344	2 4	[illegible]
19	M	33	185	32	102	62	79	93	341	2 2	66
20	M	50	215	21	111	59	81	80	303	2 0	[illegible]
21	M	57	184	20	127	75	98	58	340	2 2	41
22	M	67	232	33	130	57	82	71	32[illegible]	2 4	[illegible]
23	F	45	231	38	111	60	86	78	358	3 1	90
24	M	49	221	28	107	49	77	57	320	2 9	84
25	M	38	136	31	90	53	72	75	294	3 0	[illegible]
26	M	47	165	31	106	56	77	69	36[illegible]	2 3	[illegible]
Mean		47	196	28	108	58	80	71	332	2 5	[illegible]
± 1 S D		10	32	6	14	8	9	12	21	0 4	[illegible]
P vs Gr 1		NS	NS	< 0 001	NS	< 0 001	< 0 01	NS	< 0 01	< 0 001	NS

Abbreviations LVSP left ventricular peak systolic pressure LVEDP left ventricular end diastolic pressure SAP systolic aortic pressure DAP dias aortic pressure MAP mean aortic pressure HR heart rate during pressure recording LVET left ventricular ejection time CI cardiac index MSPG systolic pressure gradient between left ventricle and aorta AVA aortic valve area AS aortic stenosis AI aortic insufficiency cong congenital coronary artery disease LCx left circumflex coronary artery MI slight mitral incompetence VSD ventricular septal defect digital patients maintenance digitalis fao aortic regurgitant fraction Gr group S D standard deviation NS not significant (P > 0 05) P probability (unpaired t te cases in whom selective coronary arteriography was carried out

Interrelations between contractile indexes and correlations with end diastolic pressure volume and mass As shown in Figs 2 to 5 and in Table IV there was no close correlation between the isovolumic and the ejection phase contractile indexes The highest correlation coefficient (r = 0 53) was observed between mean normalized systolic ejection rate and peak measured isovolumic velocity of shortening The isovolumic as well as the ejection phase indexes were inversely related to left ventricular end diastolic pressure (Table IV) The correlation coefficients varied between −0 61 and −0 70 Significant inverse correlations but with lower correlation coefficients (−0 34 to −0 59) existed between the contractile indexes and the end diastolic volume/M² Both isovolumic contractile indexes showed significant inverse correlations with left ventricular muscle mass/M² (Figs 6 and 7, Table IV) whereas the ejection phase indexes were not correlated significantly with muscle mass

Discussion

Isovolumic vs ejection phase contractile indexes Recent studies on the usefulness of isovolumic and ejection phase indexes for evalu

AVA (cm)	Diagnosis	Comments
0 35	AS	digital.†
0 65	AS AI	fao 0 06
1 4	AS cong	
0 7	AS	†
0 3	AS	†
1 0	AS	†
0 6	AS	†
1 5	AS cong	
1 1	AS AI	fao 0 18
0 75	AS cong	
1 6	AS AI	fao 0 28†
0 7	AS	†
0 9	AS AI	fao 0 2[illegible]†
0 8	AS AI VSD	fao 0 11 † L-R shunt 26%
0 8	AS	†
0 6	AS	digital.†
1 2	AS AI	fao 0 09†
0 88		
0 38		
0 9	AS AI	fao 0 50†
0 45	AS AI MI	fao 0 [illegible]0† digital
0 5	AS AI	fao 0 30† digital
0 4	AS CAD	sten LCx 70" †
0 7	AS AI	fao 0 33† digital
0 5	AS AI	fao 0 12 digital.
0 8	AS AI	fao 0 [illegible]8
1 0	AS AI MI	fao 0 41†
1 0	AS AI	fao 0 46† digital
0 69		
0 [illegible]		
NS		

ating left ventricular contractile function have yielded conflicting results In patients with compensated and decompensated left ventricular volume overload pressure overload or cardiomyopathy total pressure Vmax was found to be the most sensitive indicator of myocardial performance and showed a more consistent relationship to clinical congestive failure than the ejection fraction [9] Similar conclusions with respect to sensitivity of indicating depressed left ventricular function can be drawn from the work of Graham and associates because these authors reported a significantly reduced total pressure Vmax in a group of pediatric patients with a chronic pressure overload of the left ventricle in whom the ejection fraction was within the normal range In other series of pediatric patients with various forms of left ventricular disease total pressure Vmax[20] and peak measured velocity of the contractile elements[8] were generally depressed when abnormal left ventricular dynamics based on a decreased ejection fraction an increased end diastolic volume or increased end diastolic pressure were present In individual patients there was however overlap between the group considered to have normal cardiac function and that with abnormal conventional left ventricular dynamics Using the same criteria in addition to a normal cardiac index and absence of asynergy for defining normal left ventricular function Peterson and associates found that mean velocity of circumferential fiber shortening and mean normalized systolic ejection rate separated almost completely the subjects of a control group of normal persons from those of an abnormal group comprising patients with diffuse myocardial involvement In contrast to mean velocity of circumferential fiber shortening and mean normalized systolic ejection rate total pressure Vmax and peak measured isovolumic velocity of shortening showed some overlap between the patients in the normal and the abnormal group Thus the authors concluded that the ejection phase contractile indexes appear to offer a preferable mode for assessing myocardial function in the basal state Similarly Kreulen and associates[21] reported the isovolumic contractile indexes Vce 10 and Vmax calculated with developed pressure to be significantly less sensitive than ejection fraction end-diastolic pressure or the presence of asynergy in detecting left ventricular dysfunction in patients with various forms of congenital valvular myocardial and coronary artery diseases These findings are not surprising since developed pressure contractile indexes have been previously demonstrated to be considerably less sensitive than total pressure indexes for detecting abnormal left ventricular function [9, 5]

In the present study that was carried out in a series of patients with one predominant abnormal hemodynamic feature i e chronic pressure overload from aortic stenosis neither the isovolumic nor the ejection phase contractile indexes proved to be clearly superior for identifying depressed left ventricular contractile function although slightly more patients were found to have reduced isovolumic than reduced ejection phase indexes The largest number of patients was however detected to have abnormal contractile function when the isovolumic and the ejection phase

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17	M	34	217	16	160	76	114	70	325	4 7	[illegible]
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19	M	33	185	32	102	62	79	93	341	2 2	[illegible]
20	M	50	215	21	111	59	81	80	303	2 0	[illegible]
21	M	57	184	20	127	75	98	58	340	2 2	[illegible]
22	M	67	232	33	130	57	82	71	325	2 4	[illegible]
23	F	45	231	38	111	60	86	78	358	3 1	[illegible]
24	M	49	221	28	107	49	77	57	320	2 9	[illegible]
25	M	38	136	31	90	53	72	75	294	3 0	[illegible]
26	M	47	165	31	106	56	77	69	365	2 3	[illegible]
Mean		47	196	28	108	58	80	71	332	2 5	[illegible]
± 1 S D		10	32	6	14	8	9	12	24	0 4	[illegible]
P vs Gr 1		NS	NS	< 0 001	NS	< 0 001	< 0 01	NS	< 0 01	< 0 001	[illegible]

Abbreviations LVSP left ventricular peak systolic pressure LVEDP left ventricular end diastolic pressure SAP systolic aortic pressure DAP dia[illegible] aortic pressure MAP mean aortic pressure HR heart rate during pressure recording LVET left ventricular ejection time CI cardiac index M PG [illegible] systolic pressure gradient between left ventricle and aorta AVA aortic valve area AS aortic stenosis AI aortic insufficiency cong congenital [illegible] coronary artery disease LCx left circumflex coronary artery MI slight mitral incompetence VSD ventricular septal defect digital patients [illegible] maintenance digitalis fao aortic regurgitant fraction Gr group S D standard deviation NS not significant (P > 0 05) P probability (unpaired t te[illegible] cases in whom selective coronary arteriography was carried out

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AV4 (cm)	Diagnosis	Comments
0 3	AS MI	digital †
0 8	AS AI	fao 0 3?†
1 0	AS AI	fao 0 10
0 7	AS AI	fao 0 33
0 75	AS AI	fao 0 20
0 5	AS	†
0 9	AS	digital †
0 6	AS AI	fao 0 14†
0 65	AS AI	fao 0.35†
0 69		
0 ?1		
NS		
NS		
0 4	AS	
1 4	AS AI	fao 0 20†
0 4	AS AI	fao 0 05 digital
0 6	AS	†
0 7	AS AI	AI slight digital †
0 6	AS AI	fao 0 1? digital †
0 68		
0 37		
NS		
NS		
NS		

versely affected the intrinsic inotropic state of the individual contractile units and therefore to have led to the decrease of the isovolumic afterload independent contractile indexes in Group 3 When muscle mass becomes very much increased as in Group 2 the intrinsic level of contractility decreases further In this situation the strength of over all left ventricular contraction cannot be maintained and the ejection phase indexes decrease as well Thus it appears that the dimi nution of the ejection phase indexes may be the consequence either of an insufficient development of myocardial mass at an essentially normal intrinsic level of contractility or of an impairment of intrinsic contractility in severe hypertrophy This view is corroborated by the regression analyses between left ventricular muscle mass and the ejection phase parameters (Table IV) that showed no statistically significant correla tions In contrast Vmax and Vpm showed signif

Table IV Linear regression analyses and correla tion coefficients (41 cases)*

y	*x*	*r*	*P*	*Regression equation*
V_r	Vpm	0 43	< 0 01	y = 0.545 + 0 588x
V_{cf}	Vmax	0 46	< 0 00?	y = 0 497 + 0 479x
MNSER	Vpm	0 53	< 0 001	y = 1 197 + 0 775x
MNSER	Vmax	0 50	< 0 001	y = 1.244 + 0.561x
Vpm	LVEDP	−0 70	< 0 001	y = 1 751 − 0 0276x
Vmax	LVEDP	−0 65	< 0 001	y = 2 260 − 0 034?x
V_{cf}	LVEDP	−0 61	< 0 001	y = 1.910 − 0 0332x
MNSER	LVEDP	−0 65	< 0 001	y = 2.872 − 0 0375x
Vpm	EDVI	−0 59	< 0 001	y = 1 705 − 0 00484x
Vmax	EDVI	−0 48	< 0 005	y = 2.119 − 0 00?18x
V_{cf}	EDVI	−0 34	< 0 05	y = 1 648 − 0 00382x
MNSER	EDVI	−0 38	< 0 02	y = 2 596 − 0 00451x
Vpm	LMMI	−0.57	< 0 001	y = 1 7?1 − 0 00336x
Vmax	LMMI	−0.53	< 0 001	y = 2.251 − 0 00411x
V_{cf}	LMMI	−0 29	NS	
MNSER	LMMI	−0.30	NS	

Abbreviations V_{cf} mean velocity of circumferential fiber shortening (circ /sec) MNSER, mean normalized systolic ejection rate (EDVs/sec.) Vpm, peak measured velocity of shortening of the contractile elements (ML/sec) Vmax maximal extrapolated velocity of short ening of the contractile elements (ML/sec) LVEDP left ventricular end-diastolic pressure (mm. Hg) EDVI left ventricular end-diastolic volume index (mL/M) LMMI left ventricular muscle mass index (Gm /M) r correlation coefficient P probability NS not signi ficant.

icant inverse correlations with left ventricular muscle mass (Figs 6 and 7) This finding lends evidence for the contention that hypertrophy per se is a determinant of intrinsic myocardial contractility[22 ?]

Significance of left ventricular end-diastolic pressure as an indicator of left ventricular func tion While according to the traditional hemody namic concept an increased left ventricular end diastolic pressure was thought to be associated with ventricular dysfunction it is now recognized that an increased left ventricular end diastolic pressure in the presence of an increased afterload and myocardial hypertrophy does not necessarily indicate reduced contractile function[25] The percentage of the patients with chronic left ventricular pressure overload in whom an in creased end-diastolic pressure is accompanied by a normal contractile function is however not known In the present study seven of the 17 patients with both the isovolumic and the ejec tion parameters within the normal range (Group 1) showed an increased left ventricular end diastolic pressure (> 14 mm Hg)[26] Conversely

Table III cont'd

Case No	Sex	Age (yr)	LVSP (mm Hg)	LVEDP (mm Hg)	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	HR (beats/min)	LVET (msec)	CI (L/min M²)	MSPG (mm Hg)
Group 3 (ejection phase indexes normal isovolumic indexes depressed)											
27	M	51	243	19	152	79	111	71	294	2 0	83
28	M	53	196	25	121	74	93	81	289	2 7	62
29	M	30	206	12	126	82	112	67	345	4 0	63
30	M	35	246	31	133	62	99	76	330	2 4	85
31	M	28	209	25	122	73	95	59	325	2 8	63
32	M	46	209	19	114	70	91	64	322	2 2	68
33	M	44	175	19	109	76	86	63	295	2 6	45
34	M	53	231	14	135	77	98	66	324	2 7	58
35	M	52	199	27	111	50	68	53	367	2 4	69
Mean		44	213	21	125	71	95	67	321	2 6	70
± 1 S D		10	23	6	14	10	13	9	26	0 6	14
P vs Gr 1		NS	NS	< 0 01	NS	NS	NS	NS	NS	< 0 01	NS
P vs Gr 2		NS	NS	< 0 05	< 0 05	< 0 01	< 0 02	NS	NS	NS	NS
Group 4 (isovolumic indexes normal ejection phase indexes depressed)											
36	F	31	251	28	131	83	104	79	311	3 9	109
37	M	60	181	17	145	65	98	55	370	4 3	44
38	M	59	221	23	126	65	90	63	341	2 2	[illegible]
39	M	63	216	15	142	66	100	68	307	3 2	[illegible]
40	M	61	220	21	126	67	96	65	342	3 6	82
41	F	56	235	14	128	69	93	61	320	2 3	83
Mean		55	221	20	133	69	97	65	332	3 3	81
± 1 S D		12	23	5	8	7	5	8	24	0 9	21
P vs Gr 1		NS	NS	< 0 05	NS	NS	NS	NS	< 0 02	NS	NS
P vs Gr 2		NS	NS	< 0 02	< 0 01	< 0 02	< 0 001	NS	NS	< 0 05	NS
P vs Gr 3		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

contractile indexes were combined for the assessment Thus it would appear that in contrast to patients with diffuse myocardial involvement[9] left ventricular contractile function in aortic stenosis is best evaluated by considering both the isovolumic as well as the ejection phase parameters

Discordance between isovolumic and ejection phase parameters Influence of left ventricular mass The discordance between the isovolumic and the ejection phase parameters in Groups 3 and 4 needs some further comments In the face of a chronic pressure burden the increase in muscle mass is essential for maintaining the strength of over all left ventricular contraction and hence for preserving a normal extent and velocity of fiber shortening On the other hand, the development of pressure hypertrophy may lead per se to a decrease of contractile state, since in isolated cardiac muscles from animals with hypertrophy, produced by pressure overloading of several weeks[22 24] the maximal velocity of shortening was found to be significantly reduced as compared to that of control animals Thus hypertrophy appears to have beneficial as well as detrimental consequences for the left ventricular dynamics In Group 3 of the present study left ventricular wall thickness and muscle mass were higher than in Group 4 although the differences did not reach significance Nevertheless, it may well be that at similar loading conditions reflected by almost identical average aortic valve areas (Table III) the greater muscle mass in Group 3 allowed to keep both mean V_{cf} and MNSER within normal limits whereas the extent of hypertrophy in Group 4 was insufficient to cope with the increased pressure burden resulting in decreased ejection phase parameters On the other hand the more pronounced hypertrophy in Group 3 than in Group 4 is likely to have ad

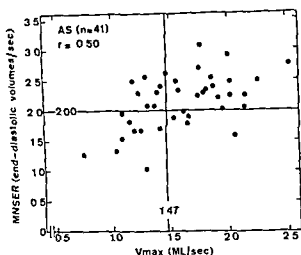


Fig 5 Relationship between mean normalized systolic ejection rate (ordinate) and maximal extrapolated velocity of shortening of the contractile elements (abscissa) in 41 patients with aortic stenosis (*AS*) The horizontal and the vertical lines indicate the lower limits of normality for MNSER and Vmax respectively Discordance between the two contractile indexes was observed in 13 of 41 cases (upper left and lower right quadrants)

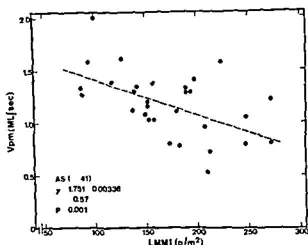


Fig 6 Relationship between peak measured velocity of shortening of the contractile elements (ordinate) and left ventricular muscle mass index (abscissa) The correlation is significant although not close

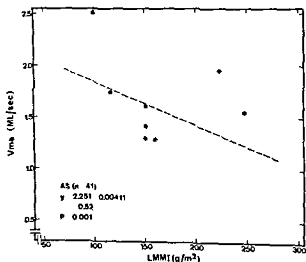


Fig 7 Relationship between maximal extrapolated velocity of shortening of the contractile elements (ordinate) and left ventricular muscle mass index (abscissa) There is a loose inverse correlation similar to that in Fig 6

correlation coefficient between these two vari ables than 0.65 (Table IV) would have been expected This lack of a close correlation is also documented by the fact that normal (Group 4) and clearly depressed (Group 3) values for Vmax and Vpm were found to be associated with almost identical average values of end diastolic pressure (Table III) Furthermore it is evident from Figs 6 and 7 that the actual values of the isovolumic total pressure indexes are dependent on left ventricular muscle mass Thus it appears that in the basal state Vmax is influenced by determi nants other than end diastolic pressure and may therefore provide a more global picture of contractile function than the single measurement of end diastolic pressure

Summary

This study is to reappraise the usefulness of isovolumic as compared to ejection phase indexes for detecting abnormal left ventricular contrac tile function in patients with a common hemody namic abnormality namely chronic left ventric ular pressure overload In 41 subjects with pure or predominant aortic stenosis left ventricular pres sure measurements were performed by microma nometry Single plane left ventricular cineangio grams were carried out in the right anterior oblique (RAO) and the A P position The isovo lumic contractile indexes we used in this study were peak measured velocity of shortening of the contractile elements (Vpm) and Vmax obtained from linear extrapolation of total pressure velocity curves The end diastolic and end systolic RAO cineventriculograms served for the calculation of the ejection phase parameters mean velocity of circumferential fiber shortening (V_{cf}) and mean normalized systolic ejection rate (MNSER) Of the 41 patients Vpm was de

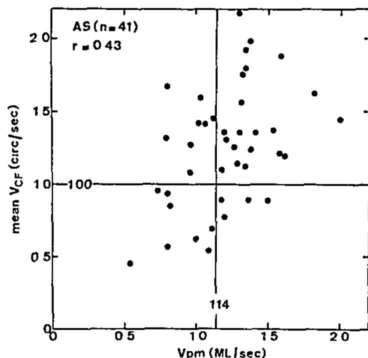


Fig 2 Relationship between mean velocity of circumferential fiber shortening (ordinate) and peak measured velocity of shortening of the contractile elements (abcissa) in 41 patients with aortic stenosis (*AS*) The horizontal and the vertical lines indicate the lower limit of normality for mean V_{CF} and Vpm respectively Note that in 12 cases (upper left and lower right quadrants) there was discordance between the two indexes in characterizing left ventricular contractile function

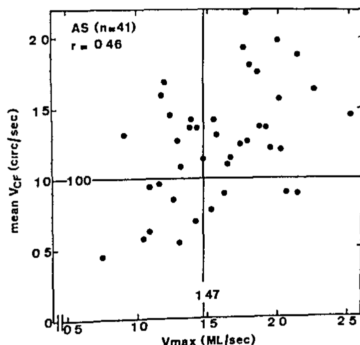


Fig 3 Relationship between mean velocity of circumferential fiber shortening (ordinate) and maximal extrapolated velocity of shortening of the contractile elements (abcissa) in 41 patients with aortic stenosis (*AS*) The horizontal and the vertical lines indicate the lower limit of normality for mean V_{CF} and Vmax respectively Discordance between the two contractile indexes was observed in 13 of 41 cases (upper left and lower right quadrants)

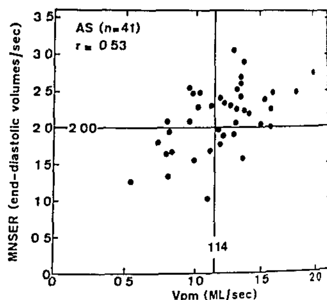


Fig 4 Relationship between mean normalized systolic ejection rate (ordinate) and peak measured velocity of shortening of the contractile elements (abscissa) in 41 patients with aortic stenosis (*AS*) The horizontal and the vertical lines indicate the lower limits of normality for MNSER and Vpm respectively Then in 12 patients (upper left and lower right quadrants) the two contractile indexes gave dissimilar answers as to normality or abnormality of left ventricular contractile function

only three patients in the remaining three group where either the isovolumic or the ejection phase parameters or both were depressed had a normal end diastolic pressure Then in the present series of patients with aortic stenosis an increased left ventricular end diastolic pressure was associated with abnormal left ventricular function in 75 per cent (21/28) and with normal left ventricular function in 25 per cent (7/28) An abnormal left ventricular function would have been missed based on a normal end diastolic pressure in 13 per cent (3/24) of the patients with documented depressed contractile indexes (Groups 2 3 and 4) This percentage may however be higher when patients on long term treatment with diuretics are evaluated

Kreulen and associates [1] have suggested that calculation of Vmax with total pressure would seem to offer little advantage over the simpler measurement of left ventricular end diastolic pressure since in acute experiments it has been shown that elevation of end diastolic pressure can in itself depress the value of Vmax when total pressure is used [27] This view appears however to be an oversimplification and this for the following reasons if total pressure Vmax is predominantly dependent on end diastolic pressure a higher

24 Cooper G., Satava R. M., Jr Harrison C E and Coleman H N Mechanism for the abnormal energetics of pressure induced hypertrophy of cat myocardium Circ Res. 33 213 1973
25 Braunwald E and Ross, J., Jr Ventricular end diastolic pressure Appraisal of its value in the recognition of ventricular failure in man Am J Med 34 147 1963
26 Mehmel, H C., Krayenbuehl H P., and Wirz P Isovolumic contraction dynamics in man according to two different muscle models J Appl. Physiol 33 409 1972
27 Grossman W., Haynes F Paraskos, J A., Saltz S., Dalen J E., and Dexter L. Alterations in preload and myocardial mechanics in the dog and in man Circ Res. 31 83 1972

pressed in 16 (39 per cent), Vmax in 17 (42 per cent), V_{CF} in 12 (29 per cent), and MNSER in 14 (34 per cent) When the isovolumic and the ejection phase parameters were combined, 24 patients (59 per cent) were found to have at least one of the four contractile indexes below normal In 26 of the 41 patients the isovolumic and the ejection phase indexes provided the same conclusions as to normality of left ventricular function In contrast, 15 patients showed discordant isovolumic and ejection phase indexes An increased left ventricular end diastolic pressure was only inconsistently related to an abnormal left ventricular function because in 7 of 28 patients with an end diastolic pressure above 14 mm Hg all contractile indexes were normal Furthermore a normal end diastolic pressure was present in three of 24 patients with depressed myocardial function

It is concluded that in chronic left ventricular pressure overload from aortic stenosis neither the isovolumic nor the ejection phase indexes are superior in sensitivity for assessing contractile function In this clinical setting the combination of both types of indexes appears to be the most reliable way for identifying patients with depressed contractile function of the left ventricle in the basal state

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REFERENCES

1 Sonnenblick E H Parmley W W and Urschel C W The contractile state of the heart as expressed by force velocity relations Am J Cardiol 23 488 1969
2 Mason D T., Spann J F Jr and Zelis R Quantification of the contractile state of the intact human heart Am J Cardiol 26 248 1970
3 Taylor R R Theoretical analysis of the isovolumic phase of left ventricular contraction in terms of cardiac muscle mechanics Cardiovasc Res 4 429 1970
4 Mason D T Braunwald E Covell J W Sonnenblick E H and Ross J Jr Assessment of cardiac contractility The relation between the rate of pressure rise and ventricular pressure during isovolumic systole Circulation 44 47 1971
5 Graham T P Jr Jarmakani J M Canent R V Jr and Anderson P A W Evaluation of left ventricular contractile state in childhood Normal values and observations with a pressure overload Circulation 44 1043 1971
6 Mirsky I Ellison R C and Hugenholtz P G Assessment of myocardial contractility in children and young adults from ventricular pressure recordings Am J Cardiol 27 359 1971
7 Karliner J S Gault, J H Eckberg D., Mullins C B and Ross J Jr Mean velocity of fiber shortening A simplified measure of left ventricular myocardial contractility Circulation 44 323 1971
8 Chatterjee K Sacoor M Sutton G C and Miller G A H Assessment of left ventricular function by single plane cineangiographic volume analysis, Br Heart J 33 565 1971
9 Peterson K. L. Skloven D Ludbrook P., Uther J B, and Ross J Jr Comparison of isovolumic and ejection phase indices of myocardial performance in man Circulation 49 1088 1974
10 Krayenbuehl H P, Rutishauser W Wirz P and Burchard D Measurement of left ventricular pressure by a transseptally introduced tipmanometer in man and determination of instantaneous dP/dt and velocity of shortening of the contractile elements by an analog calculating unit Z Kreislaufforsch 59 989 19 0
11 Sonnenblick E H Series elastic and contractile elements in heart muscle Changes in muscle length, Am J Physiol 207 1330 1964
12 Parmley W W Spann J F Jr Taylor, R R., and Sonnenblick E H The series elasticity of cardiac muscle in hyperthyroidism ventricular hypertrophy and heart failure Proc Soc Biol Med 127 606 1968
13 Maron B J Ferrans V J and Roberts W C Myocardial ultrastructure in patients with chronic aortic valve disease Am J Cardiol 35 725 1975
14 Krayenbuehl H P Rutishauser W Wirz P Amende, I and Mehmel H High fidelity left ventricular pressure measurements for the assessment of cardiac contractility in man Am J Cardiol 31 415 1973
15 Krayenbuehl H P Mehmel H C and Wirz P Doit on appliquer la pression intraventriculaire totale ou développée dans le calcul de la relation pression vitesse isovolumétrique du ventricule gauche chez l'homme? Arch Mal Coeur 67 1345 1974
16 Dodge H T Sandler H Baxley W A and Hawley R R Usefulness and limitations of radiographic methods for determining left ventricular volume Am J Cardiol 18 10 1966
17 Simon R Krayenbuehl H P Rutishauser W Steiger U Brunner H H and Schoenbeck M Evaluation of contraction performance in the normal human le ventricle (abst) Eur J Clin Invest 4 358 1974
18 Rackley C E Dodge H T Coble Y D Jr and Hay R F A method for determining left ventricular mass in man Circulation 29 666 1964
19 Falsetti, H L Mates R E Greene D G and Bunnell I L Vmax as an index of contractile state in man Circulation 43 467 1971
20 Hugenholtz P G Ellison R C Urschel C W Mirsky I and Sonnenblick E H Myocardial force velocity relationships in clinical heart disease Circulation 41 191 1970
21 Kreulen T H Bove A A McDonough M T Sands M J and Spann J F The evaluation of left ventricular function in man A comparison of methods Circulation 51 677 1975
22 Spann J F Jr Buccino R A Sonnenblick E H and Braunwald E Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure Circ Res 21 341 1967
23 Bing O H L Matsushita S Fanburg B L and Levine H J Mechanical properties of rat cardiac muscle during experimental hypertrophy Circ Res 28 234 1971

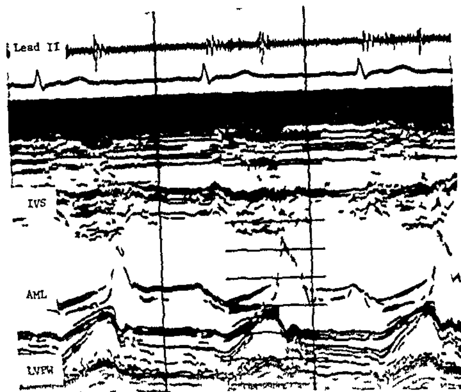


Fig 1 Normal pattern of left ventricular posterior wall motion (*LVPW*) During the isovolumetric phase of systole the left ventricular posterior wall moves slightly anteriorly or posteriorly With the onset of left ventricular ejection the posterior wall moves smoothly and rapidly in an anterior direction During diastole the posterior wall maintains a posterior position Paper speed 50 mm /sec with 1 sec time lines. *Abbreviations* IVS = interventricular septum AML = anterior leaflet of mitral valve LVPW = left ventricular posterior wall

space Once the posterior left ventricular wall was identified it was scanned along its long axis by slightly rotating the transducer so as to sweep from the mitral annulus to the posterior papillary muscle

In addition to observing the gross motion of the interventricular septum and posterior wall the timing of LVPW motion relative to electrocardiographic events was determined The interval between the onset of the QRS and the initial anterior displacement of the LVPW during systole (QPW) was measured to within 10 msec At least five cardiac cycles were examined from each patient and only those records exhibiting unbroken endocardial echoes were included

One hundred echocardiograms were randomly selected from the files of the Division of Cardiology and examined retrospectively This group consisted of normal subjects as well as a spectrum of congenital and acquired heart diseases Included in this series were patients with intraventricular conduction defects of both the right bundle branch block and left bundle branch block types All tracings were obtained with equipment identical to that used in the prospective study with recordings made at a paper speed of 50 mm / sec An additional ten subjects were studied to determine the normal QPW interval Only those echocardiograms exhibiting clear and continuous LVPW endocardial echoes were selected Paper speed was 100 mm /sec

Results

Fig 1 illustrates the normal pattern of LVPW motion In the group of ten normal controls the QPW interval measured 100 msec to 160 msec with a mean of 124 msec

Twelve patients with WPW syndrome were studied Group I consisted of seven patients with WPW type A There were five males and two females with an age range of seven to 52 years Five had no associated cardiovascular disease Subject 3 was recovering from the postcardiotomy syndrome and Subject 4 had non obstruc

Left ventricular posterior wall motion in patients with the Wolff-Parkinson-White syndrome

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The Wolff Parkinson White syndrome (WPW) has intrigued clinicians and electrophysiologists since its original description in 1930 [1] Interest has focused principally on the mechanisms underlying the electrocardiographic abnormalities and the arrhythmias characteristic of this entity Relatively little attention has been directed towards any associated mechanical alterations

Because the normal sequence of ventricular excitation is disturbed in the WPW syndrome, it is reasonable to anticipate alterations in the pattern of ventricular contraction Direct evidence supporting this supposition is scanty Previous studies utilizing a variety of invasive and non invasive techniques have yielded conflicting results [2-8] The echocardiogram provides an opportunity to study the motion of multiple cardiac structures continuously throughout the cardiac cycle It was utilized in the present study to examine the mechanical consequences of ventricular pre excitation The left ventricular posterior wall (LVPW) is readily identified during routine echocardiographic examination In the normal subject, during the period of isovolumetric contraction, the LVPW maintains a constant position relative to the anterior chest wall, or it may be displaced slightly anteriorly or posteriorly With the onset of left ventricular ejection the LVPW moves anteriorly towards the inter ventricular septum and chest wall Following completion of ejection, the LVPW returns to its previous posterior position Premature excitation of the LVPW has been demonstrated in some patients with WPW Type A [10] It was postulated that such patients might exhibit abnormalities of LVPW motion Ultrasound examination of the LVPW was employed to test this hypothesis

Methods

Patients with the WPW syndrome were identified through their records in the Division of Cardiology at the University of Maryland Hospital Others were referred from local community hospitals A twelve lead electrocardiogram was recorded and each patient was then classified as WPW type A or WPW type B according to the criteria of Rosenbaum and associates [11] The PR interval and the QRS duration were determined by examination of simultaneously recorded standard Leads I II and III The polarity of the delta wave in each lead was noted as well as the mean frontal plane QRS axis and the direction of the major QRS deflection in Leads V_1 and V_2 The presence or absence of any associated cardiac abnormalities was ascertained by physical examination and review of other available laboratory data

Echocardiograms were obtained utilizing a commercial Smith Kline Ekoline Model 20 device employing a 2 25 MHz focused transducer* with a face diameter of 5/8 inch Permanent records were recorded on an Electronics for Medicine Model VR6 strip chart recorder at paper speeds of 50 and 100 mm /sec with 0 04 sec time lines The ECG lead exhibiting the shortest PR interval was displayed with the M mode echocardiogram Patients were examined in the supine or left lateral decubitus position with the transducer in the third or fourth left intercostal

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I	V	Type WPW*		LVPW motion	QPW	IVS
+	+	A	3?	N	125	N
+	+	A	3	abn	?	N
+	+	A	3	abn	50	abn
+	+	A	4?	abn	50	N
+	+	A	3	N	120	N
+	+	A	4	N	160	N
+	+	A	3?	N	130	N
+	+	B	1	N	?	?
+	+	B	1	N	120	abn
+	+	B	2	N	120	N
+	+	B	1	N	118	N
+	+	B	1	N	136	N

sound A chest x ray demonstrated generalized cardiomegaly with increased pulmonary vascular markings. A triphasic pericardial friction rub was detected on the second hospital day An echocardiogram failed to demonstrate any significant pericardial effusion Treatment with bed rest digitalis and diuretics resulted in a sustained diuresis associated with a fifteen pound weight loss and prompt resolution of symptoms. Left ventricular posterior wall motion was then studied during normal sinus rhythm and during paced rhythm by converting the demand pacemaker to the fixed rate mode with an external magnet During sinus rhythm with anomalous conduction the abnormality of LVPW motion was prominent (Fig 4A) Fig 4B obtained during asynchronous pacing demonstrates normalization of LVPW systolic motion Fig 4C demonstrates the transition from sinus rhythm to paced rhythm and the disappearance of the LVPW abnormality During the paced rhythm the QPW interval measured from the pacemaker artifacts was 126 msec With resumption of sinus rhythm and WPW conduction the QPW interval measured 50 msec

Case 4 Intermittent WPW Type A with slow Kent bundle conduction

Patient 4 a 17 year-old male with a one year history of exercise induced palpitations, was evaluated because of syncope Physical examination revealed an irregular pulse prominent jugular A waves, and clear lungs. The apical impulse was displaced lateral to the left midclavicular line and was associated with a left ventricular lift S and S were normal, S was palpable at the apex and an S gallop was audible There were no significant murmurs nor could any be elicited by Valsalva maneuver positional changes, or amyl nitrite inhalation. The chest x ray demonstrated cardiomegaly with clear lung fields An echocardiogram was consistent with the diagnosis of asymmetric septal hypertrophy Mitral valve motion was normal. The ECG revealed WPW type A with bursts of an irregular supraventricular tachycardia (Fig. 5A) The rhythm disturbance was readily controlled with digitalis and quinidine sulfate On this regimen, the PR interval remained constant and the QRS shortened, although a small delta wave persisted (Fig 5B) The partially normalized ECG was suggestive of left ventricular hypertrophy Following carotid sinus massage the PR interval lengthened, the QRS duration increased and the delta wave assumed prominence The association of PR interval prolongation with accentuation of WPW aberration suggested that in this patient bypass conduction was slow Increased vagal tone appeared to favor AV conduction through the bypass tract by slowing or blocking conduction through the AV node Left ventricular posterior wall motion was observed to change coincident with changes in PR interval and QRS morphology During minimal bypass conduction, the PR interval was 129 msec., the QRS duration was 117 msec., and LVPW motion was normal. The interval between the onset of the delta wave and the first anterior LVPW motion (QPW) measured 155 msec. (Fig 6A) During carotid sinus massage there was slight slowing of the sinus rate prolongation of the PR interval (168 msec) and the QRS duration (139 msec) in association with a markedly accentuated delta wave The QPW interval was abbreviated (50 msec.) and a prominent anterior bulge interrupted the pattern of LVPW motion (Fig 6B)

Discussion

According to current concepts the WPW syndrome represents premature excitation of a segment of ventricular myocardium due to the presence of one or more accessory atrioventricular (AV) conduction pathways [2] The abnormal QRS morphology characteristic of this entity is principally determined by the site of insertion of the anomalous AV communication The relative conduction velocities across the normal and the accessory AV pathways and the site of the pacemaker controlling cardiac rhythm are also of importance in this regard Rosenbaum and associates[11] classified the WPW syndrome into two types based upon their electrocardiographic features Type A was characterized by a positive delta wave and a dominant R wave in Leads V_1 and V_2 In these patients it was postulated that left ventricular pre-excitation occurred by way of muscular bridge linking the left atrium with the posterior left ventricle or interventricular septum Type B was characterized by a dominant S wave in Leads V_1 and V_2 and a positive delta wave and prominent R wave in the left precordial leads It was felt to represent right ventricular pre-excitation due to an accessory communication between right atrium and right ventricle It is generally accepted that the arbitrary division of this electrocardiographic syndrome into two

Table I Clinical, electrocardiographic and echocardiographic characteristics of study group

Patient No	Age & sex	D_x	PR	QRS	Axis	QRS V_1	QRS V_1	Polarity of delta wave (leads) I	II	III	aV_R	aV_L	aV_F	V	V_1	V_1
Group I																
1	7/M	N	90	120	−48	rSR	R	+	+	+	−	+	+	+	+	+
2	34/M	N	110	110	+45	R	R	+	−	−	−	+	−	+	+	+
3	28/F	PCS	90	120	−60	RS	R	+	−	−	−	+	−	+	+	+
4	17/M	HCM	168	139	+103	R	R	+	+	+	−	−	+	+	+	+
5	52/F	N	105	135	I	R	R	+	−	−	−	+	−	+	+	+
6	25/M	N	120	130	+80	RS	RS	+	+	+	−	+	+	+	+	+
7	8/M	N	100	120	−30	rsR S	RS	+	+	−	−	+	−	+	+	+
Group II																
8	39/F	N	110	120	+89	rS	rS	+	+	+	−	−	+	+	+	+
9	47/F	N	80	120	+42	rS	rS	+	+	+	−	+	+	+	+	+
10	21/M	N	80	110	−20	rS	rS	+	−	−	−	+	−	+	+	+
11	52/M	N	120	120	+10	rS	rS	+	+	+	−	+	+	+	+	+
12	28/F	N	100	110	−20	rS	rS	+	−	−	+	+	−	+	+	+

Left hand column classification according to the criteria of Rosenbaum et al right hand column classification according to the criteria of Bo[illegible] al

Abbreviations Abn = abnormal Axis = mean frontal plane QRS axis in degrees Dx = clinical diagnosis HCM = hypertrophic cardiomy[illegible] I = indeterminate IVS = pattern of interventricular septal motion LVPW = left ventricular posterior wall N = normal PR = PR inte[illegible] milliseconds QPW = interval from onset of QRS inscription to initial LVPW systolic motion in milliseconds PCS = post cardiotomy s[illegible] QRS = duration of QRS in milliseconds

tive hypertrophic cardiomyopathy Group II consisted of five patients with WPW type B There were three males and two females with ages ranging from 21 to 52 years None of the patients with type B had any associated cardio vascular disease Table I summarizes the perti nent clinical and electrocardiographic data There were no significant differences with respect to mean QRS duration mean PR interval, mean frontal plane QRS axis or distribution of Q waves between Group I and Group II

All patients in Group II exhibited normal LVPW motion The interval between the onset of the delta wave and the initiation of LVPW anterior displacement (QPW) averaged 124 msec The pattern of interventricular septal motion was normal in three patients paradoxical in one and could not be evaluated in one patient

In contrast three of the seven patients in Group I exhibited distinctly abnormal LVPW motion This was characterized by the abrupt anterior displacement of LVPW shortly after the inscription of the delta wave (QPW in two of the three patients in whom it could be accurately measured was 50 msec), followed by a brief posterior motion, and then a second anterior movement Fig 2 is a representative echo Septal motion was normal in six patients and paradox ical in one Two patients with intermittent WPW type A were studied in more detail

A similar pattern of abnormal LVPW motion was not encountered among the 100 echocardio grams examined retrospectively, nor was it observed in the ten normal controls

Case 3 WPW Type A with left ventricular epicardial pacemaker

Patient 3 a 28 year old female had a history of WPW type A and paroxysmal tachycardia since the age of seven years Because of two documented episodes of ventricular fibrillation precipitated by atrial fibrillation with a rapid ventricular response she was considered to be a candidate for surgical interruption of the bypass tract Although electrophysiologic studies suggested the presence of a left atrial-left ventricular Kent bundle the WPW pattern was not obliterated despite an extensive incision around the left atrioventricular sulcus* As an alternative procedure the His bundle was interrupted a[illegible] an R wave inhibited left ventricular epicardial pacemaker was implanted The postoperative ECG was unchanged from those obtained preoperatively and continued to demonstrate WPW type A (Fig 3) She presented to the University of Maryland Hospital one month later with symptoms of biventricular congestive heart failure Physical examination revealed a blood pressure of 120/80 mm Hg without pulsus paradoxus, a pulse of 120 beats/min generalized edema a few basilar râles prominent jugular CV waves a Grade II/VI systolic murmur consistent with tricuspid regurgitation and a loud S gallop

*Electrophysiologic studies and surgery were performed at another institution

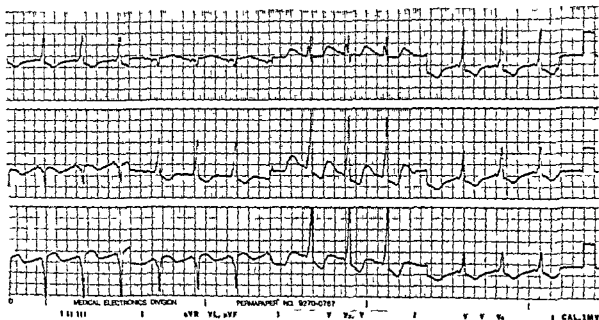


Fig 3 Twelve lead electrocardiogram Patient 3 exhibiting WPW type A

Ferrer and co workers recorded right ventricular and brachial artery pressures in two patients with WPW Both the Q RVs (interval between the onset of the QRS and the upstroke of the right ventricular systolic pressure curve) and the Q BAs (interval between the onset of the QRS and the upstroke of the brachial artery systolic pressure curve) were markedly prolonged in the patient with WPW type A whereas the patient with WPW type B exhibited minimal prolongation of Q RVs and marked prolongation of Q BAs The authors postulated the slow intramural spread of the activation wave from the point of insertion of an anomalous AV communication could account for the observed delays The different degrees of ventricular asynchronism encountered in the two patients were attributed to hypothesized differences in the site of bypass insertion and ventricular wall thickness

Dack and collegues utilized electrokymography to evaluate ventricular asynchronism in four patients with WPW They failed to note any abnormality of right or left ventricular ejection as determined by the timing of aortic and pulmonary artery pulsations with respect to electrocardiographic events They did not classify their patients as to right or left pre excitation

March and colleagues studied three patients with intermittent WPW The subject with WPW type B demonstrated paradoxical splitting of S and an earlier rise in right ventricular pressure during anomalous conduction as compared to normal conduction A second subject with WPW type A exhibited early aortic valve closure as evidenced by a premature aortic component of S and the early inscription of dicrotic notch on a carotid pulse tracing A third case type unspecified failed to demonstrate phonocardiographic changes when conduction changed from normal to anomalous Six subjects with fixed WPW patterns type unspecified were stated to have normal phonocardiograms and carotid pulse tracings Three others were reported to have wide split S with delayed pulmonic components

Zuberbuhler and Bauersfeld recorded paradoxical splitting of S_2 in three of four subjects with WPW type B and suggested that this was due to premature excitation of the right ventricle

Recently Ishikawa and colleagues[9] examined a group of 20 subjects with WPW nine type B and eleven type A with simultaneously recorded phonocardiograms apexcardiograms (ACG) and carotid pulse tracings The intervals between the onset of the P wave and the central phase of S_1 (P I) between the P wave and the central phase of S_2 (P II) and between the P wave and the upstroke of the systolic wave of the ACG (P C) tended to be shorter in patients with WPW as compared to a group of controls although the differences did not reach a level of statistical

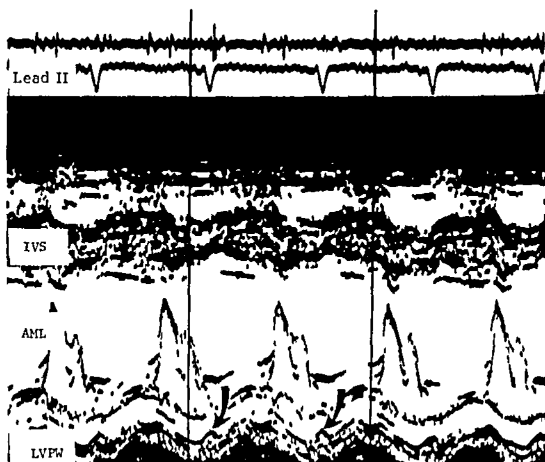


Fig 2 Abnormal pattern of LVPW motion observed in patients with WPW type A *Arrows* indicate the early anterior displacement of the posterior wall The premature bulge appears to interrupt an otherwise normal pattern of posterior wall motion Paper speed 50 mm /sec with 1 sec time lines Abbreviations same as Fig *1*

types is unsatisfactory Many intermediate cases have been reported that do not fall clearly into either category More recently Boineau and colleagues[10] published examples of five distinct ECG patterns, correlating each with a specific site of ventricular pre excitation as determined by direct epicardial mapping techniques Utilizing this classification system Group I patients manifested either left posterior or left lateral pre excitation while Group II patients manifested right anterior pre excitation as indicated in Table I Although a synchronous electrical activation has been well documented in patients with WPW its influence upon mechanical events has been more controversial

In his extensive monograph on the WPW syndrome Ohnell alluded to the possible mechanical consequences of ventricular pre excitation A jugular phlebogram obtained during the transition from junctional rhythm without pre excitation to sinus rhythm with pre excitation showed some variation Unfortunately, only a few beats are displayed considerable baseline move ment is present, and the possibility of retrograde P waves altering the wave form during junctional rhythm leads one to question the significance of the illustration Two phonocardiograms obtained during intermittent pre excitation demonstrated alterations in the amplitude and degree of split ting of the second heart sound However simult neous carotid pulse tracings were not obtained so it is not possible to tell whether right sided or left sided events were altered by the change in conduction

Kossmann and Goldberg[3] recorded phonocardiograms and carotid pulse tracings in a case of WPW type B exhibiting alternating aberrant and normal conduction During normal conduction the second sound (S) was physiologically split with the pulmonic component following the aortic component During anomalous conduction S became single and the interval between the onset of the QRS and the upstroke of the carotid pulse tracing increased Although the authors attributed the observed changes to delayed left ventricular excitation premature right ventricular excitation may have contributed to the alterations in S_2

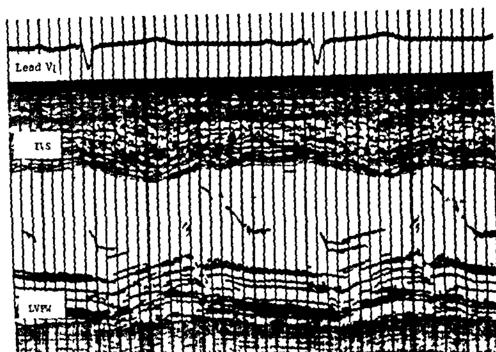


Fig 6A Patient 4 during minimal WPW aberration A small delta wave persists however a deep S wave has replaced the prominent R wave in V The pattern of LVPW motion is now normal QPW = 155 msec Paper speed 100 mm /sec with 0 04 sec time lines Abbreviations same as Fig 1

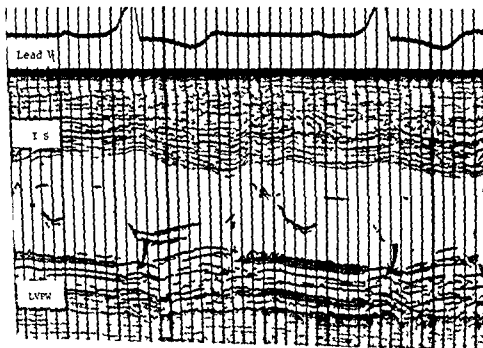


Fig 6B Patient 4 during maximal WPW aberration *Arrows* indicate premature anterior motion of LVPW QPW = 50 msec Paper speed 100 mm /sec with 0 04 sec time lines Abbreviations same as Fig 1

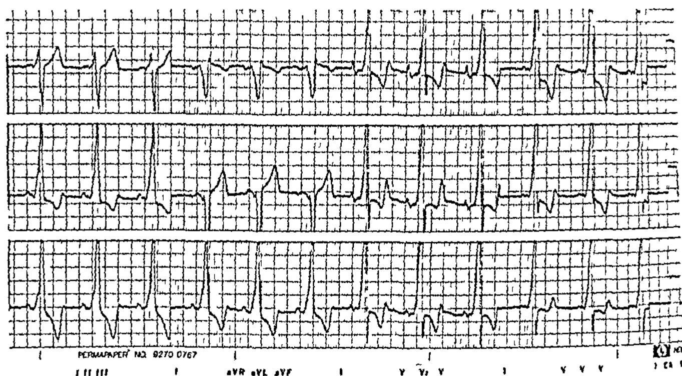


Fig 5A Twelve lead electrocardiogram from Patient 4 during maximal anomalous conduction PR interval 0 13 sec QRS duration 0 14 sec prominent positive delta wave a dominant R wave in V

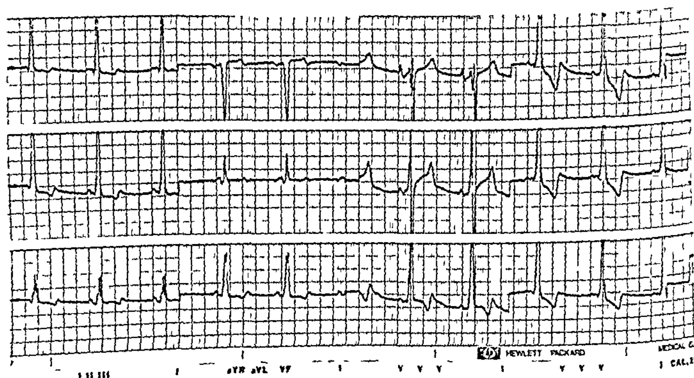


Fig 5B Twelve lead electrocardiogram from Patient 4 during minimal anomalous conduction P interval 0 13 sec QRS duration 0 12 sec small positive delta wave persists in lead V however major QRS deflection is now negative

abnormalities at a time when ventricular pre excitation was no longer present

The present study was also designed to study alterations in ventricular wall motion The results indicate that some patients with WPW type A exhibit an abnormality of left ventricular posterior wall motion in the form of premature anterior displacement of this structure The location of the area of premature contraction is consistent with the predicted site of bypass tract insertion utilizing either the criteria of Rosenbaum and colleagues [1] or Boineau and as

tion (Wolff Parkinson White syndrom) AM HEART J 29 ?81 1945
2 Moore F N., Spear J F and Boineau J P Recent electrophysiologic studies on the Wolff Parkinson White syndrome N Engl J Med 289 956 1973
3 Prinzmetal M Kennamer R Corday F Osborne J A Fields J and Smith L A Accelerated conduction The Wolff Parkinson White syndrome and related conditions Modern Medical Monographs New York, 1952 Grune & Stratton Inc p 43
4 Bandiera G and Antognetti, P F Ventricular precontracting area in the Wolff Parkinson White syndrome Demonstration in man Circulation 17 225 1958
15 Dillon J C Chang S and Feigenbaum H Echocardiographic manifestations of left bundle branch block, Circulation 49 8 6 1974
16 Ticzon A R Damato A N., Caracta A R., Russo G Foster J R and Lau S H Echocardiographic evaluation of the intraventricular septal motion during pre excitation and normal conduction in the WPW syndrome Clin Research 23 210A April, 1975

ciates[11] A similar abnormality was not encountered in patients with WPW type B nor in the control group which included a variety of intraventricular conduction defects The observation that the abnormal LVPW motion appeared and disappeared coincident with the presence and absence of anomalous conduction in patient 3 with intermittent WPW type A (Fig 4C) argues against a fortuitous or artifactual abnormality In support of this conclusion are the echocardiograms from patient 4 during minimal and maximal bypass conduction During minimal bypass conduction (Fig 6A) as evidenced by the small delta wave and predominantly normal QRS, LVPW motion was normal During maximal bypass conduction (Fig 6B) the LVPW abnormality was apparent It is likely that the mass of ventricular myocardium undergoing premature excitation is one determinant of whether or not LVPW abnormalities will be detected The failure to observe abnormal LVPW motion in four patients with WPW type A may be explained on this basis Since the ultrasound beam traverses a relatively small segment of LVPW, the finding of normal LVPW motion in some patients with WPW type A is not at all surprising

Finally, mention should be made of the pattern of interventricular septal motion in patients studied Since WPW type B superficially resembles left bundle branch block one might anticipate paradoxical septal motion in these patients[15] This has been suggested by Ticzon and colleagues[16] who observed abnormal septal motion in five patients with 'anterior right ventricle pre excitation' and in one with 'posterior right ventricle pre excitation In the present study, septal motion was normal in three of the four patients with WPW type B in whom it would be evaluated It was paradoxical in one subject with type B Six of seven patients with type A had normal septal motion One had clinical evidence of tricuspid insufficiency, which is known to be associated with paradoxical septal motion

Summary

Echocardiography appears to be a sensitive technique for detecting disturbances in left ventricular posterior wall motion in subjects with WPW type A The characteristic abnormality consists of premature anterior displacement of the LVPW shortly after the inscription of t[he] delta wave The ability to detect abnormal w[all] motion is influenced by the size of the segmen[t] [of] myocardium undergoing pre excitation the s[ite] of insertion of the anomalous pathway and [its] accessibility to echocardiographic study T[he] results of this study support the concept th[at] WPW type A represents premature excitatio[n] [of] the posterior left ventricular wall in so[me] patients Moreover, such pre excitation may b[e] associated with an altered pattern of left vent[ric]ular contraction A similar pattern of LVP[W] motion was not observed in a large group [of] randomly selected clinical echocardiograms, in[cluding] a variety of intraventricular conduct[ion] disturbances

The technical assistance of Regina Hayes and the cri[tical] comments of Dr Leonard Scherlis are gratefully ack[nowl]edged

REFERENCES

1 Wolff L Parkinson J and White P D Bundle bra[nch] block with short PR interval in healthy young peop[le] prone to paroxysmal tachycardia AM HEART J 5 6[85] 1930
2 Ohnell R F Pre excitation a cardiac abnorm[ality] Stockholm 1944 P A Norstedt & Soner p 68
3 Kossmann C E and Goldberg H H Sequence of ventricular stimulation and contraction in a case of anomalous atrioventricular excitation AM HEART J 33 308 1947
4 Ferrer M I Harvey R M Weiner H M Cathcart R T and Cournand A Hemodynamic studies in tw[o] cases of Wolff Parkinson White syndrome with parox[y]smal AV nodal tachycardia Am J Med 6 725 1949
5 Dack S Paley D H and Brahms S S The electro[cardio]mogram in Wolff Parkinson White syndrome AM HEART J 41 437 1951
6 March H W Selzer A and Hultgren H N The mechanical consequences of anomalous atrioventricular excitation (WPW syndrome) Circulation 23 587 1961
7 Zuberbuhler J R and Bauersfeld S R Paradoxical splitting of the second heart sound in the Wolff Parkin son White syndrome AM HEART J 70 595 1965
8 Ishikawa H Kagoshima T Hasegawa S Hishiki Y Yamao H Yamamoto T and Kigawa Y Wolff Parkinson White syndrome Mechanocardiographic study on the mechanical consequences of ventricular pre excitation AM HEART J 90 35 1975
9 McDonald I G Feigenbaum H and Cheng S Analysis of left ventricular wall motion by reflected ultra sound Circulation 46 14 1972
10 Boineau J P Moore F N Spear J F, and Sealy W C Basis of static and dynamic electrocardiographic variations in Wolff Parkinson White syndrome Am J Cardiol 32 32 1973
11 Rosenbaum F F Hecht H H Wilson F N, and Johnston F D The potential variations of the thorax and the esophagus in anomalous atrioventricular exci[tation]

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In the questionnaires prepared for the routine collection of data space had been provided to describe diverse functions of daily life The sections on baseline status contained a solicitation of data about the patient s customary occupation and about reasons for any modification of duties change in occupation or unemployment Inquiry was also made about the patient s performance of nonoccupational physical activities including hobbies pastimes or other interests

The questionnaires used at follow up examinations were concerned with alterations in employment with other occupational events and with changes in other physical activities The idea was to encourage both patients and physicians to note the status of these diverse activities at each periodic examination The questionnaire format was open ended[4] because no specific categories of coding had been established beforehand Our hope was that the details supplied in the data would allow suitable categories to be discerned and demarcated afterward when the total results were inspected

After the trial was completed the pertinent questionnaire forms for each patient were sent to us for analysis We deliberately did not receive or examine any associated clinical data related to anginal frequency supplementary therapy electrocardiograms roentgenograms or any other descriptions of cardiac status Our sole concern was with the information pertaining to functional capacity The data we examined contained identification digits for each patient but no detectable indication of the nature or dosage of drugs To prevent any bias during our activities all decisions and codings were conducted blindly without an awareness of therapy

Taxonomic procedures

Three different sets of coding taxonomies were developed The first set dealt with the patient s status at baseline before the period of active treatment with either timolol or placebo This baseline taxonomy was divided into three subsets referring to three different aspects of function occupation customary activities and sporadic activities A second coding taxonomy was concerned with post therapeutic change in each of these three types of functional activities A third taxonomy provided a global rating of change based on the aggregate of the alterations noted in all three aspects of function

The categories and criteria for these classifications are presented in the sections that follow To assist future users of these criteria we have included extensive examples chosen directly from the questionnaire data to show the way in which the classifications were employed

1 Baseline classification Since the transition categories described later would depend on changes in condition rather than on an arbitrary magnitude of activity the purpose of grading each patient s condition at baseline was to allow the baseline ratings to be used as stratification variables In the subsequent analysis we could divide patients into groups with different degrees of baseline impairment for each type of activity and we could then note the frequency with which post therapeutic changes occurred in the different groups The ratings for baseline status were as follows

a Occupation This class of data referred to gainful employment for men or women or to housework when pertinent for women The following ratings were employed

0 NONE No impairment of usual work

1 SLIGHTLY IMPAIRED Distinct impairment but not great enough to code as moderate because the decrease in effort or change in activity seems slight or the impairment is not clearly caused by angina *Examples* Patient with a sedentary job who is careful not to get cold housewife whose daughter has assumed heavier household duties

2 MODERATELY IMPAIRED Patient has changed jobs or reduced effort in current job because of angina *Examples* Painter changed to factory work 4 years ago because of angina and now supervises a conveyer belt line but occasionally must stop work because of an attack physiotherapist has reduced her physical activity about 80 per cent and now spends most of her time in administration housewife gets angina while

A new clinical taxonomy for rating change in functional activities of patients with angina pectoris

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When patients with angina pectoris receive long acting pharmaceutical agents the efficacy of treatment is generally appraised by counting the frequency of anginal attacks and the quantity of supplementary nitroglycerine tablets Although both these numbers can indicate a change in the patient's clinical status they do not show what has happened to the patient s ability to function in the diverse activities of daily life

An impaired functional capacity is often the main stimulus that makes an anginal patient seek treatment but changes in functional performance are seldom deliberately evaluated in reports of medical or surgical therapy The patient s capacity at baseline before treatment is given, can be rated with one of the four categories proposed by the New York Heart Association (NYHA)[1 2] *unimpaired* or *slightly moderately* or *severely impaired* Although suitable for denoting general baseline state these ratings have two major disadvantages for showing subsequent change They are concerned with overall gross function not with distinctions in different types of activity and they indicate the patient s condition at only a single point in time If used for transitions from one state to another, the four categories of the rating scale are too coarse to denote important changes that may occur while the patient remains in the same functional category For example a laborer who is unemployed because of angina may still be listed after treatment as *moderately impaired* because he remains unable to work but he may be delighted with an improvement that reduces his angina enough to allow him to play with his grandchildren A housewife who remains unable to climb stairs may be pleased that she can resume gardening

To denote changes in a patient s functional capacity a new taxonomic procedure was needed The new taxonomy would provide ratings for different types of function and for transitions in those functional states In this report we shall describe the development and application of such a taxonomy

Material and methods

The patients under analysis here were enrolled in a multicenter multinational cooperative clinical trial whose detailed design has been reported elsewhere [3] The patients were adults, 35 to 69 years of age with stable angina pectoris that had been present for at least 2 months occurring at least four times weekly in the absence of various co morbid diseases After a 4 week baseline period in which everyone was treated three times daily with placebo the patients were randomized to receive three daily doses of either 5 mg tablets of timolol maleate or an identical looking placebo given in a double blind manner

During the next 6 weeks (weeks 5 to 10 of the study) the dosage of the therapeutic agents was titrated in escalating increments to reach a level of optimum clinical effects or a maximum dosage

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The questionnaires used at follow up examinations were concerned with alterations in employment with other occupational events and with changes in other physical activities The idea was to encourage both patients and physicians to note the status of these diverse activities at each periodic examination The questionnaire format was open ended[4] because no specific categories of coding had been established beforehand Our hope was that the details supplied in the data would allow suitable categories to be discerned and demarcated afterward when the total results were inspected

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The categories and criteria for these classifications are presented in the sections that follow To assist future users of these criteria we have included extensive examples chosen directly from the questionnaire data to show the way in which the classifications were employed

1 Baseline classification Since the transition categories described later would depend on changes in condition rather than on an arbitrary magnitude of activity the purpose of grading each patient s condition at baseline was to allow the baseline ratings to be used as stratification variables In the subsequent analysis we could divide patients into groups with different degrees of baseline impairment for each type of activity and we could then note the frequency with which post therapeutic changes occurred in the different groups The ratings for baseline status were as follows

a Occupation This class of data referred to gainful employment for men or women or to housework when pertinent for women The following ratings were employed

0 NONE No impairment of usual work.

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2 MODERATELY IMPAIRED Patient has changed jobs or reduced effort in current job because of angina *Examples* Painter changed to factory work 4 years ago because of angina and now supervises a conveyer belt line but occasionally must stop work because of an attack physiotherapist has reduced her physical activity about 80 per cent and now spends most of her time in administration housewife gets angina while

doing housework and has to limit her use of the vacuum cleaner

3 SEVERELY IMPAIRED Unable to work because of angina

7 AMOUNT UNCERTAIN Patient is impaired but amount is not specified or specifiable *Example* At baseline patient is no longer employed because of both angina and some other disease or situation

8 NOT APPLICABLE Patient is beyond work age and is retired or patient is no longer working for reasons other than angina (This category would also be used for a patient who is not working because of a preceding myocardial infarction rather than because of angina itself)

9 UNKNOWN No available statement regarding patient's occupation

b Customary activities This class of data referred to walking stair climbing setting up exercises driving an automobile riding a bicycle to work or other physical activities that a particular patient would customarily perform at daily or almost daily intervals The coding scheme which was identical to that used for rating *sporadic activities* is shown in the next section

c Sporadic activities This class of data referred to gardening lawn mowing sports or any other sporadically performed activities connoting a distinct degree of physical exertion, that were not part of the patient s customary routine Completely sedentary hobbies and interests such as reading knitting and sketching were not included

The rating schemes for customary and sporadic activities had an identical structure The codes were as follows

0 NONE Patient is specifically cited as having no impairment

1 SLIGHT Distinctly impaired in at least one activity but no activities abandoned *Examples* Daily walks are now shorter and he walks more slowly, used to swim three times weekly for 30 minutes per session but now swims less often and for only 10 to 15 minutes per session

2 MODERATE Completely impaired in at least one activity, which has been abandoned *Examples* No longer rides bicycle to work, has stopped dancing at social gatherings

3 SEVERE Impairment is so substantial that no activities are performed in this category *Examples* Stays in bed or sitting most of time has given up swimming tennis table tennis a[illegible] cannot watch football on television if his own team is playing

8 AMOUNT UNKNOWN Patient is described a[illegible] impaired, but the details are not sufficient t[illegible] allow the debility to be cited in one of th[illegible] categories 1 3

9 UNKNOWN No comment made regardi[illegible] activities in this category, or no activities pe[illegible]formed for reasons other than angina

2 Changes in specific activities When th[illegible] active treatment period began, the princip[illegible] follow up examinations in this study we[illegible] conducted at 10 16 22, and 28 weeks after ons[illegible] of each patient s observation period The 10 we[illegible] results as noted earlier, would represent t[illegible] patient s status after completing the 6 week tit[illegible]tion interval for either timolol or placebo The [illegible] week results would represent the patient s fi[illegible] status 24 weeks after onset of active thera[illegible] and 18 weeks after establishment of optim[illegible] dosage

For each of these intervals, a rating of cha[illegible] was entered for each of the three aspects [illegible] function occupation customary activities [illegible] sporadic activities The same coding scheme [illegible] used for rating the changes in each type [illegible] activity The ratings were as follows

1 MAJOR DETERIORATION Although availa[illegible] this rating was not applied to any patients in [illegible] study (Patients who might have been so c[illegible]sified did not complete the clinical trial) S[illegible] hypothetical examples of the rating are for *oc[illegible]pation* patient has had to stop work becaus[illegible] angina, or housewife has become unable [illegible] perform even minimal efforts for *custom[illegible] activities* daily setting up exercises have b[illegible] abandoned completely because any exertion would cause pain and for *sporadic activities* patient has had to abandon hobby of auto repairing because pain would begin as soon as he started to work

2 SLIGHT OR MODERATE DETERIORATION Examples of this rating are for *occupation* tractor driver has taken on lighter work or market woman has reduced working hours from 30 to 18 per week for *customary activities* a patient who had been walking 4 to 6 km per day has anginal attacks again and avoids effort and for *sporadic activities* patient used to garden on weekends but has now reduced gardening activities

3 No Change

4 Slight or moderate improvement This rating was used for any improvement less than the major grade cited in the next category Examples of this rating were for *occupation* patient is now doing some tailoring at home after having stopped because of angina or housewife has done more housework with more effort without feeling pain for *customary activities* can climb more stairs now or resumed commuting to work more often by bicycle or can walk longer trips without pain and for *sporadic activities* patient now plays golf again or is painting house or is swimming 300 meters two to three times per week from baseline of 200 meters once weekly

5 Major improvement Examples of this rating were for *occupation* construction worker out of work 2 years has now resumed work as builders mate or housewife who did only a little only what is necessary has now resumed all household duties without pain for *customary activities* anginal pains are no longer provoked by hurrying up three flights of stairs and for *sporadic activities* patient attends parties as usual but now can participate once again actively dancing with only mild restriction

9 Further impairment for reasons other than angina Examples of this rating were for *occupation* patient has been laid off of construction job or has retired because of back pains and for *customary activities* the weather is not suitable for [daily] walks

3 Summary ratings of transition The individual ratings that have just been described were applied to the transitions noted in each type of activity at each of the four follow up examinations After the ratings were established for each time period a summary score was created to describe the patient s progress in each activity throughout the entire period of treatment The summary scores for each activity were derived from the individual transition ratings at each time interval The ratings used for the summary scores were as follows

0 Much worse = major deterioration (this rating although available was not necessary for any patients in this series)
1 Worse" = slight or moderate deterioration
2 No change"
3 "Better = slight or moderate improvement
4 Much better = major improvement

For these summary ratings a patient was cited as improved or as deteriorated if he had been so classified without subsequent contradiction at any of the four follow up examinations If the ratings for a particular activity fluctuated from one examination to the next the summary classification depended on the rating applied to the last follow up period at which a change was reported Patients who had further impairment that had been attributed only to nonanginal causes were rated as having *no change*

4 Global rating After these summary scores were determined for each of the three types of activity a single global rating of change was established to encompass the patient s total functional progress in all activities over all four examination periods This global rating corresponded to the general evaluation that clinical investigators are often asked to apply to a patient at the end of a study except that our ratings were based on a combination of specified entities (in the questionnaire data) rather than on a nondescript gestalt conclusion

Because of fluctuations in a patient s status at the different time intervals and because improvements in one type of function may have been counterbalanced by deterioration in another this global rating was derived from a direct judgmental evaluation of the total information The judgments were easy to make if the observed changes in all activities went in the same direction If contradictions occurred so that a patient improved in one type of activity while deteriorating in another the judgments depended on a relative weighting of the amount of change and the importance of the activity For example a minor improvement in customary activities might counterbalance a minor deterioration in sporadic activities to produce a net result of *no change* A major improvement in customary activities would outweigh a minor deterioration in sporadic activities to produce a net result of *slight improvement* Because occupation was regarded as more important than sporadic activities a slight deterioration in occupational status would outweigh a slight improvement in sporadic activities to produce a net result of *slight deterioration*

The codes for the global rating were the same five categories that had been employed for the summary rating They ranged from 0 which

Table I Occupation Transitions in functional status

Degree of baseline impairment	Summary of change				Total	Percent improved*
	Worse	No change	Better	Much better		
None	2	69	11	1	83	(14%)
Slight	0	9	0	1	10	(10%)
Moderate	1	59	12	5	77	(22%)
Severe	1	57	6	5	69	(16%)
Amount uncertain	0	16	1	0	17	(6%)
Not applicable	0	46	2	0	48	(4%)
Unknown	0	1	4	0	5	(80%)
Total	4	257	36	12	309	(16%)

*Includes patients who were either "better" or "much better."

Table II Customary activities Transitions in functional status

Degree of baseline impairment	Summary of change				Total	Percent improved*
	Worse	No change	Better	Much better		
None	1	27	6	0	34	(18%)
Slight	0	25	20	5	50	(50%)
Moderate	1	9	5	0	15	(33%)
Severe	0	13	7	4	24	(46%)
Amount uncertain	0	36	17	3	56	(36%)
Unknown	1	109	18	2	130	(15%)
Total	3	219	73	14	309	(28%)

*Includes patients who were either "better" or "much better."

represented major deterioration (or "much worse") to 4 which represented major improvement (or "much better").

5 Statistical analyses All proportions (or percentages) were compared with the *chi square* test. Statistical significance was *established* whenever, with a two sided (or "two tailed") interpretation the level of P was below 0.05. To avoid constant repetition of the phrase "statistically significant" we have often used only the term "significant" in the subsequent text.

Results

After all the cited taxonomic ratings had been determined and coded for each patient we obtained the treatment schedule and identified the individual therapeutic regimens. The coded data were then punched on *Hollerith* (IBM)

Table III Sporadic activities Transitions in functional status

Degree of baseline impairment	Summary of change				Total	Percent improved*
	Worse	No change	Better	Much Better		
None	1	24	9	0	34	[illegible]
Slight	1	27	16	1	45	[illegible]
Moderate	1	14	8	0	23	[illegible]
Severe	0	11	2	0	13	[illegible]
Amount uncertain	1	47	4	0	52	[illegible]
Unknown	1	125	16	0	142	[illegible]
Total	5	248	55	1	309	[illegible]

*Includes patients who were either "better" or "much better."

cards, the punched results were verified and the data were analyzed with the aid of an electronic sorter.

1 General findings Of the 195 patients who were randomly assigned to each of the two treatment groups at the start of the trial 15 patients in the placebo group were later dropped because of increase in angina, 12 patients were dropped because of other cardiovascular events and [illegible] because of miscellaneous reasons. In the timolol group two patients were dropped for increase in angina, 10 for other cardiovascular events and 19 for miscellaneous reasons. The two treatment groups thus had similar rates of drop out due to other cardiovascular and miscellaneous reasons, but the placebo group had a much higher rate of drop out due to worsened angina. The percentages of patients who did not complete the study because they had an increase in angina were [illegible] per cent (15/195) for the placebo group and 1.0 per cent (2/195) for timolol. This significant difference immediately suggests that timolol was an efficacious agent.

For two patients, one in each treatment group, functional status questionnaires were not completed. Our analysis of change in functional activities was therefore confined to the remaining 309 patients (146 placebo and 163 timolol) who completed the entire 28 week period of the clinical trial.

2 Changes in specific activities In the accompanying statistical tabulations (Tables I to III) we have listed the baseline conditions of the patients and the frequency of the associated subsequent changes as summarized for each type of activity. Table I is concerned with occupa-

onal status Table II with customary activities and Table III with sporadic activities These tabulations have been prepared for all patients without regard to therapy to show the way the patients were distributed according to their ratings before and after treatment

The following features of these three tables seem most noteworthy

a The results show the wide spectrum in type and degree of functional impairment that can be found in a group of anginal patients together with the wide spectrum of responses that can occur after institution of therapy

b As might be expected in an analysis of data originally collected in routine questionnaires that did not contain all the specifications needed for subsequent coding substantial amounts of information could not be categorized At baseline the quantity of missing or uncertain information was relatively small for occupational status For customary activities however the baseline assessment was unknown for about one third of the patients and uncertain for about one sixth An analogous problem of somewhat similar proportions occurred in the specifications for baseline impairment of sporadic activities

c The changes that occurred in each form of activity seemed generally unrelated to the degree of impairment at baseline An unexpected finding was the occurrence of improvements in patients who had previously denied any baseline impairment The probable explanation for such phenomena is that many patients had not been aware of a reduction in activities until the activities were later expanded after treatment

Since the post therapeutic responses were not overtly dependent on baseline status and since the changes could be classified for everyone the analyses of therapeutic efficacy would not be affected by baseline uncertainties For those analyses the patients baseline impairment in each type of activity was therefore consolidated into four categories *none* *impaired* (for any known degree of impairment) *indeterminate* (or *uncertain*) and *unknown* These are the categories used to describe baseline status in subsequent tables

3 Changes in functional status *in relation to* treatment Our next step was to see whether the improvement rates for each of the three types of activity were related to the associated treatment The results for all three types of activity are assembled and presented in the three vertical sections of Table IV In each of these sections the denominators refer to treated patients who had the cited degree of baseline impairment in the cited activity at baseline The numerators refer to the number of patients whose transition in the cited activity had received a summary rating of either *better* or *much better* The associated percentages represent the rate of improvement for patients in that category The three parts of the table are discussed separately in the sections that follow

Table IV Type of treatment and rate of improvement for three types of activity

Degree of baseline impairment in cited activity	*Percentage of patients in baseline category who showed improvement in that activity*					
	Occupational status		*Customary activities*		*Sporadic activities*	
	Timolol	*Placebo*	*Timolol*	*Placebo*	*Timolol*	*Placebo*
None	11/45 (24%)	1/38 (3%)	5/17 (29%)	1/17 (6%)	7/17 (41%)	2/17 (12%)
Impaired	24/89 (27%)	5/67 (7%)	28/42 (67%)	13/47 (28%)	18/43 (42%)	9/38 (24%)
Indeterminate or uncertain	1/28 (4%)	2/37 (5%)	9/27 (33%)	11/29 (38%)	0/21 (0%)	4/31 (13%)
Unknown	0/1 (0%)	4/4 (100%)	14/77 (18%)	6/53 (11%)	13/82 (16%)	3/60 (5%)
Total	36/163 (22%)	12/146 (8%)	56/163 (34%)	31/146 (21%)	38/163 (23%)	18/146 (12%)

a Change in occupational status The total results for occupational status in Table IV show a 22 per cent rate of improvement in the timolol group—a value significantly higher than the 8 per cent in the placebo group This significant difference in post therapeutic improvement rates was also noted separately for patients whose occupational status was known at baseline to be definitely impaired or not impaired In the impaired group 27 per cent of the timolol patients improved whereas only 7 per cent of the placebo patients did so in patients with no initial impairment the improvement rates were 24 per cent for timolol and 3 per cent for placebo

b Change in customary activities The customary activities section of Table IV shows that the total improvement rate for timolol was 34 per

Table V Treatment and global change in functional status*

Treatment	Global change in total functional status				Total
	Worse	*No change*	*Better*	*Much better*	
Timolol	5 (3%)	75 (46%)	64 (39%)	19 (12%)	163 (100%)
Placebo	3 (2%)	99 (68%)	42 (29%)	2 (1%)	146 (100%)
Total	8 (3%)	174 (56%)	106 (34%)	21 (7%)	309 (100%)

Over all $\chi^2 = 21.27$ $P < 0.001$ (3 d f) χ^2 for linear trend = 15.98 $P < 0.001$ (1 d f)

Table VI Treatment gender, and global change in functional status

Treatment	Global change in total functional status				Total
	Worse	*No change*	*Better*	*Much better*	
Men					
Timolol	3 (3%)	54 (46%)	45 (38%)	15 (13%)	117 (100%)
Placebo	2 (2%)	78 (72%)	27 (25%)	2 (2%)	109 (100%)
Total	5 (2%)	132 (58%)	72 (32%)	17 (8%)	226 (100%)
Women					
Timolol	2 (4%)	21 (46%)	19 (41%)	4 (9%)	46 (100%)
Placebo	1 (3%)	21 (57%)	15 (41%)	0 (0%)	37 (100%)
Total	3 (4%)	42 (51%)	34 (41%)	4 (5%)	83 (100%)

Table VII Timing of improvement after treatment

Treatment	Week 10	Week 16	Week 22	Week 28	Total
Number and percentage of patients with any type of improvement at cited point in time					
Timolol	50 (31%)	56 (34%)	58 (36%)	64 (39%)	163
Placebo	19 (13%)	27 (18%)	31 (21%)	31 (21%)	146
Timing of first reported improvement in patients who improved					
Timolol	50 (60%)	14 (17%)	8 (10%)	11 (13%)	83
Placebo	19 (43%)	12 (27%)	7 (16%)	6 (14%)	44

cent, which was significantly higher than the 21 per cent found for placebo The differences in favor of the active treatment vs placebo are particularly striking when the analysis is confined to patients in whom a distinctive degree of impairment has been noted at baseline Such patients had an improvement rate of 67 per cent with timolol and 28 per cent with placebo In contrast to occupational improvement the improvement in customary activities appeared related to the existence of initial impairment. Improvement occurred in 41 (46 per cent) of the 89 impaired patients, but in only six (18 per cent) of the 34 patients with no initial impairment

c *Change in sporadic activities* The rightmost section of Table IV shows that the total improvement rate in sporadic activities was significantly higher for timolol (23 per cent) than for placebo (12 per cent) In subgroups of patients with either no impairment or definite impairment the timolol improvement rates were also substantially higher than the placebo rates

d *General comments* The results of Table IV indicate that timolol was superior to placebo in producing distinctive post therapeutic improvement for all three types of activity The differences were particularly apparent in patients whose baseline status could be definitely classified as either impaired or unimpaired

4 Global change ratings The global change ratings which provide a composite assessment of total functional status are presented in Table V These results are not stratified for the corresponding baseline status because we did not prepare a global score for baseline condition Since none of the patients showed major deterioration a single *worse* category was used for those who had slight or moderate deterioration A global change rating of *better* or *much better* was attained by 51 per cent (83/163) of patients in the timolol group and by 30 per cent (44/146) in the placebo group The differences between timolol and placebo were statistically significant, not only by ordinary chi square test but also by chi square test for linear trend in ordinal data

In Table VI the global results of Table V are subdivided according to the gender of the patients The previously noted global trends for superiority of timolol over placebo are maintained separately in men and in women but the difference was large enough to be significant only in men One interesting facet of the analysis is the occurrence rate of placebo reactors —the pa

ients who improved while receiving placebo This rate was 27 per cent (29/109) in men and 41 per cent (15/37) in women The difference does not reach the customary level of statistical significance (χ = 2 55 P < 0 2)

II 5 Timing of change In assembling the data reported in Tables I to IV we listed a patient as *improved* if such a change had been noted post therapeutically regardless of the time when the improvement was reported In Table VII we have analyzed two aspects of the chronologic pattern of improvement The upper part of the table shows the percentage of patients who were recorded as improved at the different times of examination For example 50 (31 per cent) of the 163 patients who received timolol were recorded as improved at week 10 and 64 (39 per cent) were recorded as improved at week 28 etc These tabulations probably underestimate the incidence of improvement For example when a patient was cited as improved at week 16 the investigator may not have repeated the same set of entries at week 2? which was left blank in the questionnaire

The lower part of Table VII is confined to indicating the time of the first noted improvement in the 127 patients who improved For example in the timolol group 60 per cent of the 83 patients who were going to have a functional improvement showed first evidence thereof at week 10 In the placebo group 70% of the 44 who were going to improve had their improvement recorded by the end of week 16 The results suggest that about one half to two thirds of the patients who were destined to show functional improvement with antianginal therapy did so within the first 2 months after therapy was instituted On the other hand a substantial proportion of patients did not begin to show improvement until several months of treatment had elapsed

Discussion

The word *scale* is often used for an array of categorical values that provides a classification or set of ratings for a particular phenomenon In customary forms of scientific measurement the scale is a series of numerical dimensions such as those used to express height weight or age For other forms of scientific expression the scale is a semiquantitative group of ordinal rankings such as the common medical ratings of *0 1+ 2+ 3+* and *4+* In another type of scale the ratings consist of nominal values that have no ranked order Such scales are used to express gender as *male* or *female* and to express occupation as *doctor lawyer merchant* or *other*

All of the scales that have just been cited are unitemporal they refer to the state of the observed entity at a single point in time For many types of scientific measurement however the phenomenon to be noted is a bitemporal transition from one state to another This transition can be readily expressed if the basic entity is measured in a dimensional scale We can simply subtract the first value of height weight or age from the second value and the difference would indicate the change in values

On the other hand if the basic entity is expressed in an ordinal scale a transition cannot readily be noted by subtracting one value from another The act of subtraction is not mathematically authorized if the scale contains arbitrary ratings rather than measured dimensions[6] More importantly although a dimensional scale contains an unlimited number of categories an ordinal scale seldom contains more than a few The few available categories may not allow suitable expression for changes that are distinctive but too small to alter the original categorical value Consequently the magnitude of a transition often cannot be determined by subtraction of values in an ordinal scale and certain significant transitions can occur without producing a simultaneous change in the original scalar value

Among the well known ordinal scales used for unitemporal classification of a patient s functional state the Katz Index of Independence in Activities of Daily Living has eight categories and the Karnofsky Burchenal Performance Index has 10 categories Because of the abundance of categories these scales might be satisfactory for denoting transitions although Karnofsky[9] later developed a different scale of ratings specifically for changes in status The Katz and the Karnofsky Burchenal scales have been used however mainly for patients with a variety of often severe physical disabilities and medical ailments The scales are less pertinent for relatively simple issues in exertional capacity The only current rating system for the functional state of patients with heart disease is the NYHA scale This scale however contains only four categories making it unable to provide adequate expression for many changes in function

In the work reported here we have established and applied a set of scales that form a "transition taxonomy" for rating the changes in different aspects of functional capacity. Although employed for transitions in patients with angina pectoris the procedure need not be restricted to cardiac disease. The same taxonomy could also be used for indicating the progress of patients with diverse other chronic ailments that impair functional capacity.

A remarkable aspect of the cited distinctions is that they could be discerned from information collected in routine questionnaires containing an "open format" without specific listings for detailed categories to be checked by the investigator. Because the necessary categories had not yet been established when this clinical trial began the questionnaires had a sectional rather than specificational format.[4] Specific sections of the questionnaire were allocated for different types of physical activity, but within each section, the investigators could report the pertinent descriptions in whatever verbal details seemed appropriate. Now that a taxonomy of transitions is available future questionnaires can be constructed with the categories of the coding taxonomy listed as a series of multiple choices to be designated appropriately. A structured questionnaire would also tend to minimize the amount of missing or unrecorded data.

The results obtained during this new analysis provide additional documentation to augment the more conventional evidence reported elsewhere that has shown the antianginal efficacy of timolol. The main question that might be raised about the therapeutic comparisons performed in both the current and the previous analyses is whether or not the clinical observers were truly double blind. Because the beta blocking action of timolol may produce bradycardia the patient's pulse rate might act as a signal that "unmasks" the identity of the therapeutic agent. Aware of the treatment a clinician may then consciously or subconsciously provide additional encouragement or exhortation to patients receiving the active drug rather than placebo.

The technique of using two sets of clinical observers—one set to regulate the patient's dosage the other set to be kept blind and to perform the history taking—would not necessarily solve the problem. During the acquisition of informed consent for the study the patient might learn about the bradycardia of beta blockade and might thereby be able subsequently to "unmask" his therapy. Furthermore unless communication between the patient and the clinician who acts as dosage regulator is restricted to a level far below the requirements of satisfactory care the patient will inevitably be affected by what is transmitted during the interchange.

The possibility that treatment may be unmasked seems unavoidable in any double blind placebo controlled clinical trial concerned with the efficacy of beta blocking agents. In order to prevent the active drug from being unmasked by bradycardia the placebo group would have to receive an agent that produces bradycardia. Because such an agent would necessarily be a cardioactive drug rather than an inert placebo the absolute efficacy of the beta blocking agent could not be determined. The comparison could deal only with the relative efficacy of the beta blocking agent and bradycardic agent. Furthermore the type of escalating dosage that is carried out to achieve an optimal level of beta blockade would be difficult or impossible to conduct in a double blind manner for a comparative agent that is deliberately chosen for its ability to produce bradycardia. Increasing doses of timolol do not produce an increase in bradycardia,[5] but an increased dose of the comparative agent might lead to its unmasking through further reductions in heart rate.

Because of these problems, the current methods for double blind comparison of beta blockers vs placebo seem to be as satisfactory a method for assessing antianginal efficacy as can be achieved within the pragmatic limitations of clinical practice. The main reassurances available to a critical analyst of the research are previous results[5] showing that the decrease in heart rate with timolol was seldom a striking phenomenon in individual patients and that the percentage reduction in pulse rate was not correlated with other clinical responses to timolol.

Our main purpose in this study, of course, was not to evaluate the therapeutic efficacy of a particular pharmacologic agent. Instead we wanted to show that changes in functional capacity can be appraised and used as an index of therapeutic efficacy. If specific inquiries are made about different activities in daily life and about changes in those activities, the assembled information can be classified coded and analyzed. By developing a transition taxonomy for expressing the results we hope that this vital clinical information will begin to receive increased attention in future analytic appraisals of therapeutic effects.

This type of clinical analysis has often been regarded as scientifically unappealing because the data are "soft" depending on subjective performances and reports by the patient. For angina pectoris however almost all of the clinical phenomena are "soft." The existence of the malady itself cannot be identified unless it is subjectively described by a patient who is also the sole source of information about the angina's diverse manners of provocation cessation, relief, intensity frequency and periodicity. All of the ailment's functional consequences involve the way that the patient can regulate or decide to regulate the various physical and emotional challenges of daily living. If angina pectoris is to be analyzed in a way that acknowledges the angina at all the investigator must be prepared to deal with soft data and to use suitable methods for "hardening" the soft data.

Many investigators today prefer to avoid the soft information entirely replacing it with the objective precise dimensional data obtained from ergometric tests with a treadmill bicycle or other technologic device Such data are obviously a desirable adjunct in evaluating the exercise capacity of an anginal patient but the data do not offer a panacea for the problems of evaluating treatment The ergometric test requires special equipment that has many disadvantages The equipment is costly in purchase and in the time it consumes for the personnel who operate it The apparatus may not be available in the many medical settings where angina pectoris is treated To yield precise reproducible results the apparatus and its operating procedure must be carefully standardized—a desideratum that has not yet become ubiquitous[9] Even when available and standardized however the procedure may not be convenient or suitable for application to all anginal patients and many patients who receive a baseline measurement may be unwilling or unable to return for the specified schedule of follow up tests Finally even if all these difficulties were surmounted there would still remain the fundamental problem of the limited scope of the data The ergometric test indicates a patient s performance in the particular set of conditions under which the test is conducted It does not indicate how the patient will respond to the challenges of lifting a weight mounting a steep flight of stairs walking in cold weather engaging in sexual activity reacting to emotional stimuli or coping with other events of daily life

An ergometric test provides an excellent measurement of a single aspect of the patient s physiologic capacity The test has played and will continue to play a useful role in the assessment of antianginal therapy The chief concern of many patients with angina pectoris however is a limitation of the ability to perform the diverse physical activities that are an integral part of living If treatment is aimed at clinically improving the patient s total functional capacity rather than altering an isolated physiologic dimension clinicians will need additional indexes to assess what happens to the patient s functional capacity

Summary

The treatment of patients with angina pectoris is commonly evaluated according to such indexes as the frequency of anginal attacks quantity of supplemental nitroglycerin and exercise performance in an ergometric laboratory test None of these indexes demonstrates the clinical change in ordinary functional limitations that may have been the major reason why a patient sought medical help The New York Heart Association ratings of functional capacity do not refer to different types of activity and the four categories of the scale are too coarse to show distinct changes that can occur while a patient retains the same rating

A new taxonomy has been devised for rating transitions in functional capacity as noted in three different kinds of functional performance occupation customary activities and sporadic activities The ratings of change in these three activities can be combined into a single global rating When applied to conventional questionnaire data for 309 patients in a randomized double blind therapeutic trial the new classifications showed a statistically significant superiority in each type of functional transition and in the global ratings for patients receiving timolol maleate rather than placebo

By augmenting the conventional information used for therapeutic evaluation the new taxonomic indexes can expand the scientific scope of antianginal treatment Data derived from history taking can be just as statistically significant as harder forms of information while simultaneously being more pertinent for the clinical challenge of choosing and evaluating the agents used in patient care

Timolol maleate having the trade name Blocadren" was originally tested as product MK 950 by Merck, Sharpe and Dohme International Division We thank Drs David Brailovsky and Ian Miller for permission to publish these data

REFERENCES

1 Criteria Committee of the New York Heart Association Diseases of the heart and blood vessels Nomenclature and criteria for *diagnosis, ed.* 6 Boston 1964 Little Brown & Company pp 112 113
2 Criteria Committee of the New York Heart Association Diseases of the heart and blood vessels Nomenclature and *criteria for* diagnosis ed. 7 Boston 1973 Little Brown & Company p 286
3 Brailovsky D Timolol maleate (MK 950) A new beta blocking agent for the prophylactic management of angina pectoris *in* Magnani, B *editor* Beta adrenergic blocking *agents* in the management of hypertension and angina pectoris New York 1974 Raven Press
4 Feinstein A R Taxonorics. II Formats and *coding systems* for data processing Arch. Intern Med. **126** 1053, 19 0
5 Feinstein A R Clinical *biostatistics.* XV The process of prognostic stratification (Part 1) Clin Pharmacol. Ther **13** 442 19/2

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This type of clinical analysis has often been regarded as scientifically unappealing because the data are "soft," depending on subjective performances and reports by the patient. For angina pectoris, however, almost all of the clinical phenomena are "soft." The existence of the malady itself cannot be identified unless it is subjectively described by a patient who is also the sole source of information about the angina's diverse manners of provocation, cessation, relief, intensity, frequency, and periodicity. All of the ailment's functional consequences involve the way that the patient can regulate or decide to regulate the various physical and emotional challenges of daily living. If angina pectoris is to be analyzed in a way that acknowledges the angina at all, the investigator must be prepared to deal with soft data and to use suitable methods for "hardening" the soft data.

Two variants of concealed trigeminy

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Schamroth and Marriott[1,2] have described two forms of concealed ventricular extrasystoles One type which they termed concealed bigeminy was characterized by an odd number of sinus beats between extrasystoles that is the number of conducted sinus beats S between extrasystoles satisfied the equation S = 2n −1 where n is any positive integer The second type of concealed extrasystoles was designated concealed trigeminy" The values of S for this disturbance satisfied the equation S = 3n −1 i e S = 2 5 8 11 *etc*

Although the precise mechanisms responsible for these forms of concealed extrasystoles are not known we have recently proposed that concealed bigeminy and trigeminy are manifestations of a 2 1 and a 3 1 block respectively in a re entry loop[3] In that study we described three variants of the classical form of concealed bigeminy The present report describes two variants of concealed trigeminy that have been detected as the result of analyzing long rhythm strips obtained in *three* patients with frequent unifocal premature ventricular activations In each of the patients the coupling intervals were variable and some fusion beats were observed however careful analysis of the interectopic intervals failed to yield any least common denominator characteristic of parasystole Therefore the premature ventricular activations are considered to have been extrasystoles

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Electrocardiographic (ECG) analyses

Case 1 Figs 1 and 2 were recorded from a 40 year old woman who had numerous unifocal ventricular extrasystoles that appeared to be related to excessive coffee ingestion and cigarette smoking The four segments of Fig 1 are continuous and represent a portion of a long rhythm strip that contained 47 consecutive ventricular extrasystoles The numbers of conducted sinus beats S between extrasystoles in Fig 1 all satisfy the equation S = 3n −1 Therefore this sequence constitutes an interval of classical concealed trigeminy If the binomial distribution is used to test the null hypothesis of a random distribution of the values of S the likelihood of six successive values of S that satisfy the above equation is remote (P = 3 [illegible])

Another section of the same rhythm strip is shown in Fig 2 the four segments are continuous It will be noted that none of the values of S satisfies the equation for classical concealed trigeminy however all values of S in Fig 2 fit the equation S = 3n For these six values of S the same null hypothesis enunciated above would also have to be rejected (P = 3 [illegible]) i e it is extremely unlikely for six consecutive values of S that fit the equation S = 3n to *occur* on the basis of chance alone

The values of S for the 46 consecutive interectopic intervals that were analyzed for this patient are compiled in Table I It may be noted that about three-fourths of the values of S belong in the category of classical concealed trigeminy (S = 3n −1) and the remaining values of S fit the equation S = 3n There was not a single value of S which satisfied the equation S = 3n −2 Out of a total of 46 values of S the possibility of obtaining zero values of S = 3n −2 on the basis of

6 Stevens S S Mathematics measurement and psychophysics *in* Stevens S S editor Handbook of experimental psychology New York 1951 John Wiley & Sons Inc pp 1 49
7 Katz S Ford A B Maskowitz R W Jackson B A and Jaffe M W Studies of illness in the aged The index of ADL A standardized measure of biological and psychosocial function J A M A **185** 914 1963
8 Karnofsky D A and Burchenal J H The clinical evaluation of chemotherapeutic agents in cancer *in* MacCleod C M editor Evaluation of chemotherapeutic agents Symposium held at the New York Academy of Medicine New York N Y 1948 New York 1949 Columbia University Press pp 191 205
9 Karnofsky D A Meaningful clinical classification of therapeutic responses to anticancer drugs, Clin Pharmacol Ther **2** 709 1961
10 Redwood D R Rosing D R., Goldstein R E Beiser D G and Epstein S F Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris Circulation **43** 618 1971

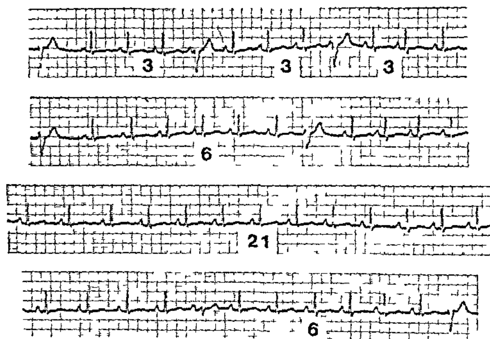


Fig 2 Another section of the rhythm strip from case 1 The four strips are continuous All values of S satisfy the equation $S = 3n$

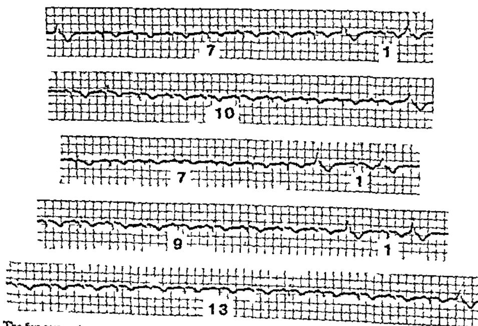


Fig 3 The five segments are a continuous portion of a long rhythm strip from case 2 All values of S except one ($S = 9$) satisfy the equation $S = 3n - 2$

cealed trigeminy namely that $S = 3n - 1$ In each case however there were numerous exceptions to the criterion In case 1 all the exceptions satisfied the equation $S = 3n$ In the other two cases, almost all of the exceptions fit the equation $S = 3n - 2$ We propose that these exceptional values of S still constitute forms of concealed trigeminy i.e they represent one of two variants of the classical form of this arrhythmia

Classical concealed trigeminy In a previous study [3] we proposed that concealed trigeminy was a manifestation of a 3 1 block in a re-entry loop In Fig 5 a short section of the ECG from case 1 with an accompanying ladder diagram will illus

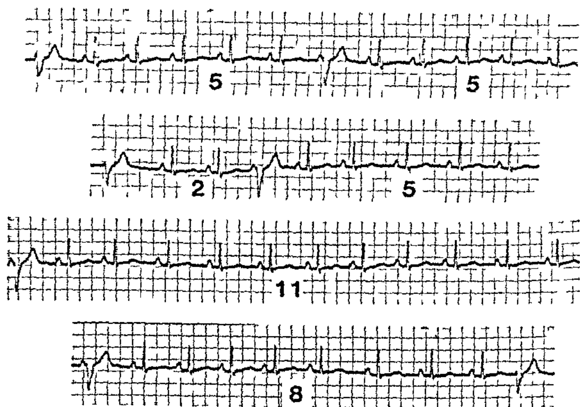


Fig 1 The four segments are a continuous portion of a long rhythm strip from case 1 The numbers of conducted sinus beats (S) between extrasystoles are indicated on the tracings All values of S satisfy the equation S = 3n –1 for the classical form of concealed trigeminy

chance alone is infinitesimally small ($P = 3^{-46}$)

Case 2 This patient was a 50 year old man with acute myocardial infarction, who developed frequent unifocal ventricular extrasystoles The distribution of the numbers of conducted sinus beats in a rhythm strip containing 145 interectopic intervals is compiled in Table I It may be noted that approximately half the values of S for this patient satisfy the equation for the classical form of concealed trigeminy There were several sequences in which numerous consecutive values of S satisfied that equation including one sequence of 17 consecutive values ($P = 3^{-17}$) and another of 14 consecutive values ($P = 3^{-14}$) On the other hand, slightly less than half of the values of S for this patient constituted exceptions to the equation for classical concealed trigeminy It may be noted in Table I that of these exceptions, almost all values of S satisfied the equation S = 3n –2 and only 2 1 per cent (three out of 145) fit the equation S = 3n Based on the null hypothesis that all exceptions to the equation S = 3n –1 would be evenly distributed between the other two equations the probability of a ratio of 45 5 to 2 1 occurring on the basis of chance alone is infinitesimally small ($P \simeq 2^{-33}$)

Fig 3 shows a segment of the rhythm strip from this patient, the five sections are continuous Of the eight interectopic intervals in the figure all but one (S = 9) satisfied the equation S = 3n –2 (i e S = 1, 4 7, 10 13 etc) Based on the null hypothesis of a random distribution of the values of S the likelihood is small of obtaining at least seven out of eight values which satisfy the equation S = 3n –2 on the basis of chance alone (P = 0 002)

Case 3 Fig 4 is a section of the rhythm strip of a 44 year old man with frequent ventricular extrasystoles Just as in the previous patient classical concealed trigeminy was the dominant rhythm, and the majority of exceptional values of S satisfied the equation S = 3n –2 In the three continuous segments in Fig 4 all seven values of S satisfied the equation S = 3n –2 ($P = 3^{-7}$) As shown in Table I of the 61 interectopic intervals analyzed in the rhythm strip from this patient, only 4 9 per cent (three out of 61) of the values of S satisfied the equation S = 3n In a patient in whom the predominant rhythm is classical concealed trigeminy the probability of obtaining a ratio of 26 3 to 4 9 for the exceptional values of S on the basis of chance alone is extremely small (P = 0 002)

Discussion

In each of the three ECG s analyzed in this study there were substantial sections (e g Fig 1) which fulfilled the criterion for classical con

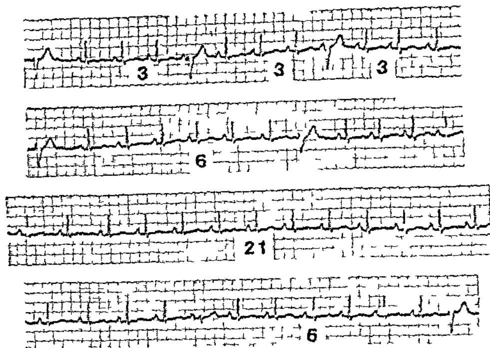


Fig 2 Another section of the rhythm strip from case 1 The four strips are continuous *All values of S satisfy the equation $S = 3n$*

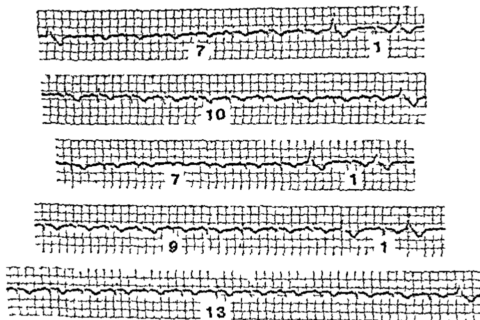


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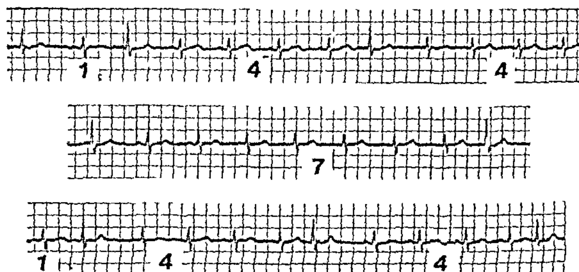


Fig 4 The three segments are a continuous section of a long rhythm strip from case 3 All values of S satisfy the equation S = 3n −2

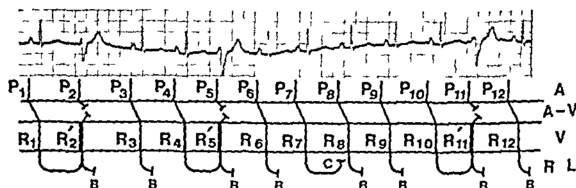
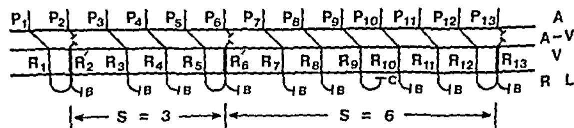
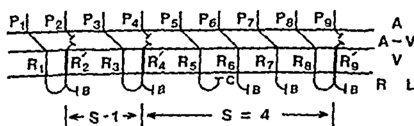


Fig 5 A section of the rhythm strip from case 1 in this portion of the strip all values of S conformed to the equation for the classical form of concealed trigeminy For the two interectopic intervals shown S = 2 and S = 5 The ladder diagram indicates the proposed course of the cardiac impulses through the atria (A) atrioventricular junction (A V) ventricles (V) and re entry loop (R L) Ventricular extrasystoles are denoted as R′ In the re entry loop are postulated two sites of block B a site of 3 1 block and C a site of "concealment" that is distal to B



3n VARIANT



3n−2 VARIANT

Fig 6 Ladder diagrams to illustrate the proposed mechanisms for the "3n" and "3n −2" variants of concealed trigeminy The abbreviations are the same as for Fig 5

te the postulated mechanism for classical trigeminy After the first normal ...ntricular activation (R_1) the impulse traverses ...e re entry loop (R L) and produces extrasys ...le R_2 The impulse immediately begins to circle ...e loop a second time but is blocked at some site which is a locus of 3 1 block The next sinus ...tivation (R_3) is also blocked at site B After the ...xt sinus activation (R_4) however the re ...ntrant impulse is conducted past the site of 3 1 ...lock (B) and an extrasystole (R) ensues Hence ...e interectopic interval between R_2 and R_5 ...ontains two conducted sinus activations (R_3 and ...) i e R R R R constitutes a sequence of ...anifest trigeminy

After extrasystole R the impulse again begins ...o circle the re entry loop but is blocked at B ...lock occurs again at this 3 1 site after the next ...inus impulse (R) After activation R the ...mpulse passes the 3 1 site but is evidently con...cealed at some site distal to B This site of ...oncealment C must be distal to B or the 3 1 ...lock sequence at B would be disturbed and the ...attern of distribution of the values of S would no ...onger conform to the equation for classical ...oncealed bigeminy The mechanisms responsible ...or concealment are not known with certainty It may simply be a block in the re entry loop similar to the phenomenon occurring at B Alternatively it may represent a propagation time around the re entry loop which exceeds the R R interval In the bottom strip of Fig 2 for example the extrasystole that terminates the sequence of 21 sinus beats is a fusion beat It occurs very late in the cycle just before the next normal ventricular activation begins If the coupling interval reflects the propagation time about the re entry loop had that propagation time been slightly longer that extrasystole in the bottom strip of Fig 2 would have been concealed

Returning to Fig 5 the two sinus impulses (R and R_4) that follow the concealed *re entrant* impulse after R are ultimately blocked at the 3 1 site B in the re entry loop After activation R however the re entrant impulse is conducted past B and is not concealed because an extrasystole (R) is evident Thus the combination of 3 1 block at B for re entrant impulses R R R and R and concealment of impulse R leads to a value of S = 5 which is consistent with classical concealed trigeminy Had re entrant impulse R been concealed and impulses R and R blocked

Table 1 The distributions of the numbers of conducted sinus beats in consecutive interectopic intervals in three patients with unifocal ventricular extrasystoles in whom the predominant pattern was classical concealed trigeminy

No of sinus beats	*Formula*	*Case No*		
		1	*2*	*3*
1	3n−2	0	8	2
2	3n−1	9	18	26
3	3n	5	0	2
4	3n−2	0	14	11
5	3n−1	9	44	11
6	3n	[illegible]	1	1
7	3n−2	0	26	3
8	3n−1	13	9	1
9	3n	0	1	0
10	3n−2	0	13	0
11	3n−1	2	3	1
12	3n	0	0	0
13	3n−2	0	3	0
14	3n−1	1	0	1
15	3n	0	0	0
16	3n−2	0	0	0
17	3n−1	0	0	2
18	3n	0	1	0
19	3n−2	0	1	0
20	3n−1	1	0	0
21	3n	1	0	0
22	3n−2	0	1	0
23	3n−1	0	1	1
24	3n	0	0	0
Total		46	145	61
	3n−2 %	0.0	45.5	26.3
	3n−1 %	76.1	52.4	68.8
	3n %	23.9	2.1	4.9

at B complete traversal of the loop by impulse R would have yielded a value of S = 8 which would also satisfy the equation S = 3n −1

3n variant The variants of classical concealed trigeminy can be explained on the basis of slight variations of the above hypothesis To account for the 3n variant it is necessary only to propose that just after each manifest extrasystole the block at site B becomes 4 1 temporarily At all other times the block is 3 1 just as in the classical form of this arrhythmia The precise reasons for such a transient shift in the block ratio have not been established however it is well known that the arterial blood pressure declines rapidly during the compensatory pause and then it increases abruptly as a consequence of the large stroke volume ejected during the postextrasystolic beat The associated alterations in

coronary perfusion pressure or the reflexly induced changes in cardiac neural activity might be responsible for a change in the block ratio just after each manifest extrasystole

The postulated manner in which a transient 4 1 block accounts for the 3n variant of concealed trigeminy is illustrated in the upper half of Fig 6 After the first extrasystole (R′), with a 4 1 block at site B, the first re entrant impulse to penetrate beyond this site would be that associated with R. If this impulse completes the loop and elicits an extrasystole (R'_4) the value of S would be 3 This manifest extrasystole would again lead to a 4 1 block at B If the next re entrant impulse (R) to penetrate beyond B is concealed (site C) subsequent re entrant impulses are again blocked at site B, but in a 3 1 ratio until another manifest extrasystole is evoked In the figure the next two re entrant impulses (after R_{10} and R_{11}) are blocked at B and the third (after R,) completes the loop to produce extrasystole R'_{11} The combination of a single 4 1 block sequence followed by one 3 1 block sequence yields a value of S = 6 Had the re entrant impulse after R, been concealed, another sequence of 3 1 block would have resulted in a value of S = 9 Additional sequences of 3 1 block would yield values of S = 12 15 18 etc, i e S = 3n Thus the combination of an initial sequence of 4 1 block followed by any number of sequences of 3 1 block would produce the 3n variant of concealed trigeminy

3n 2 variant The 3n–2' variant as exemplified by Figs 3 and 4, may be explained by a slightly different variation of the mechanism for concealed trigeminy It may be postulated that immediately after an extrasystole the block at B is 2 1, at all other times it is 3 1 as shown in the bottom half of Fig 6 Again the mechanism is not known, but the temporary conversion to a 2 1 block immediately after the manifest extrasystole may be related to hemodynamic or reflex factors

In the first interectopic interval in the bottom half of Fig 6 for example let the re entrant impulse be blocked at B after extrasystole R'_2 If the impulse is conducted past B during the activation (R_3) terminating the compensatory pause an extrasystole (R_4) may occur after only one conducted sinus beat (i e S = 1) If a similar sequence of 2 1 block at site B occurs af extrasystole R'_4 but if re entrant impulse R_5 is concealed resumption of a 3 1 block ratio at B would lead to a value S = 4, provided impulse R completes the loop Had impulse R_8 been concealed, block of impulses R_9 and R_1 at B would have yielded the value S = 7, as long as impulse R_{11} completed the loop Addition sequences of 3 1 block would have yielded values of S = 10 13 16 etc Thus a 2 1 block at B immediately after an extrasystole but a 3 1 block thereafter would lead to values of S = 3n – ?

Summary

Long rhythm strips were analyzed from three patients with frequent unifocal ventricular extrasystoles The predominant rhythm in each patient was concealed trigeminy, i e the number of conducted sinus beats S, between extrasystoles satisfied the equation S = 3n –1, where n is any positive integer In one of these patients about one fourth of the values of S did not satisfy the equation, however all such exceptional values of S satisfied the equation S = 3n In the other two patients very few of the exceptional values of S fit the equation S = 3n but they did conform to the equation S = 3n – 2 It is proposed that in all forms of concealed trigeminy, there is a characteristic 3 1 block in the re entry loop that is responsible for the extrasystoles Furthermore it is postulated that immediately after each manifest extrasystole the 3 1 block is converted transiently to a 4 1 or 2 1 block in the 3n and '3n–2 variants respectively After the first penetration of the block site after a manifest extrasystole if the re entrant impulse is concealed the 3 1 ratio is resumed in both variants until the next manifest extrasystole appears

REFERENCES

1 Schamroth L and Marriott H J L Concealed ventricular extrasystoles Circulation 27 1043 1963
2 Schamroth L The physiological basis of ectopic ventricular rhythm A unifying concept S Afr Med J Suppl 3 1971
3 Levy M N Adler D S and Levy J R Three variants of concealed bigeminy Circulation 51 646 1975
4 Daniel W W Biostatistics A foundation for analysis in the health sciences New York 1974 John Wiley & Sons Inc pp 58 64

ıiagnostic and prognostic significance of electrocardiographic nd CPK isoenzyme changes following coronary bypass urgery Correlation with findings at one year

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Perioperative myocardial infarction associated with coronary artery bypass grafting has been reported with a frequency ranging from 8 to 58 per cent [1-4] The majority of patients who die during the immediate postoperative period have evidence of acute myocardial infarction at autopsy [1] However many patients who have electrocardiographic (ECG) and/or enzyme descriptors of acute infarction have a subsequently benign clinical course [5] Identification of those patients having acute infarction following coronary artery bypass grafting has been difficult due to the lack of specificity of total enzyme elevations and ST T wave changes on ECG and the lack of sensitivity of QRS changes The cardiac specific hybrid isoenzyme of creatine phosphokinase (CPK MB) has been found to be a very sensitive indicator of myocardial necrosis and to be useful in the postoperative period following coronary artery surgery [6,7] It appears to be unaffected by skeletal muscle trauma hemolysis external cardioversion and the pulmonary and hepatic dysfunction of cardiac failure

This study was designed to determine the relationships between postoperative descriptors of acute myocardial infarction and the subsequent clinical course Documentation of left ventricular contraction pattern and cardiac performance was obtained by elective recatheterization 1 year following coronary artery bypass grafting

Materials and methods

Patient selection Patients were studied prospectively and the 103 who met the following criteria were included in the study population (1) coronary artery bypass grafting during 1972 for relief of angina without concurrent ventricular or valvular surgery and (2) preoperative Duke catheterization within 2 months prior to surgery Two patients died during surgery and the remaining 101 had serial postoperative ECG and CPK isoenzyme determinations One patient was included who had diagnostic QRS changes of infarction but in whom serial CPK isoenzymes could not be obtained Four of these patients died during the postoperative period and four more died after hospital discharge leaving 93 available for follow up evaluation Personal physicians refused recatheterization of nine (10 per cent) of these on the basis of Australia antigen four severe peripheral vascular disease three congestive heart failure one recent MI one An additional 19 (20 per cent) were not willing to undergo recatheteri

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zation Patients were contacted through their private physicians by phone or letter and the restudy protocol was explained to them Informed consent was obtained from all patients prior to cardiac catheterization Thus 65 of the 93 available patients (70 per cent) returned for elective cardiac catheterization and cardiac evaluation between 9 and 15 months (mean 13 months) after surgery The remaining 25 patients who did not undergo recatheterization did not differ significantly in symptomatic relief of angina postoperatively or in the incidence of descriptors of perioperative infarction from those who returned for restudy

Preoperative evaluation All patients had preoperative 12 lead ECG s Fifty four of the 65 patients subsequently restudied (83 per cent) had multistage maximal treadmill exercise testing[11] 25 patients had positive tests and nine patients had negative tests The remaining 20 patients had negative results but failed to achieve 85 per cent of the maximal predicted heart rate these studies were considered inadequate for interpretation Complete left and right heart catheterizations were done in all patients and included hemodynamic measurements before left ventricular cineangiography and coronary arteriography Biplane left ventricular cineangiography was performed in 23 patients and single plane (25° RAO) in 42 patients

Operative technique Aortocoronary saphenous vein grafts were used in 63 patients and internal mammary artery grafts in two patients In all but two patients extracorporeal circulation was utilized a bubble oxygenator was used with mild hypothermia (30 to 32° C) moderate hemodilution, and induced ventricular fibrillation The aorta was intermittently cross clamped in 23 patients for an average total time of 20 minutes The left ventricular was vented by insertion of a plastic drainage catheter through a small apical stab wound The wound was closed by a purse string suture and buttressed with a Teflon pledget Three patients were vented through the right superior pulmonary vein no venting was necessary in the two patients in whom extracorporeal circulation was not used Fourteen patients received three grafts 30 patients received two grafts and the remaining 21 patients received one graft

Immediate postoperative evaluation Serial postoperative ECG s were recorded once daily for all patients They were interpreted witho knowledge of enzyme or catheterization data a categorized as follows unchanged from preopera tive tracing, QRS changes persisting througho the postoperative period which were indicative c infarction[12], QRS changes indicative of cond tion disturbance generalized ST segment elev tion, localized ST segment elevation ST segment depression, T wave inversion

Plasma samples for determination of to CPK and CPK isoenzymes were obtained ro tinely over a 5 day period as follows the evenin of surgery (usually 6 hours postoperatively) A M and 6 P M the day after surgery and then a 24 hour intervals through the fourth postopera tive day

Total activity of CPK was measured by the method of Rosalki[13] using the Eskalab Clinical Chemistry System * The upper limit of normal with the Eskalab System is 130 international units per liter (I U /L)

The method used for the electrophoretic sepa ration and subsequent quantitation of the CPK isoenzymes has been described[14] This method couples CPK activity with that of hexokinase and glucose 6 phosphate dehydrogenase to yield fl o rescent nicotinamide adenine dinucleotide phos phate (NADPH) at the zones of enzyme activity The reduced NADPH produced is directly pro portional to the CPK activity in the serum and i the basis for the quantitation of the CPK Mr form

One year postoperative evaluation Complete left and right heart catheterizations were carried out electively in all 65 patients 1 year (± months) after surgery and included hemody namic measurements before left ventricul cineangiography as well as coronary arteriogra phy Degree of obliquity and tube to table to distance were similar in pre and postoperative studies No stress tests were performed dur catheterization Biplane left ventricular cinean giography was done in 58 patients and single plane in seven patients Comparisons of RA projections on all 65 patients were performed a were comparisons of LAO views in the 23 patient in whom these were available from both studie Left ventricular contraction patterns were ana lyzed by superimposing the outlines of their end systolic and end diastolic silhouettes and compar ing them with similar drawings from the preoper

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ative ventriculograms. The basal and middle thirds of the left ventricle were subdivided into anteroseptal, anterolateral, posterior and inferior quadrants and the apical third was considered as a unit. All areas of abnormal contraction demonstrated on the drawings were also confirmed by viewing the cine in motion at a projection rate of 16 frames per second. The diagrams of these cines were then analyzed by two independent observers and the areas of asynergy were classified as hypokinesia, akinesia, or dyskinesia according to the definition of Herman and associates.[1] Two of the cine pairs could not be adequately evaluated because of presence of premature ventricular beats. Among 63 pairs of pre- and postoperative ventriculograms analyzed, there was no disagreement between the two observers as to the presence or absence of asynergy. However, there were seven minor differences in classifying the type of asynergy. These cines were again reviewed and the consensus of both observers was used.

All patients had an ECG at 1 year which was analyzed along with all interim records for evidence of myocardial infarction. Sixty-three patients (97 per cent) had a multistage maximal treadmill exercise test at 1 year. Twenty-eight of these had tests which were considered adequate for interpretation both before and 1 year after surgery.

Patients were divided into functional Classes I to IV for angina and for heart failure on the basis of the New York Heart Association classification.[15]

Results

Nine patients died before their 1 year surgical anniversary. Two of these deaths were noncardiac. Of the remaining seven, two (29 per cent) had QRS changes diagnostic of myocardial infarction in the immediate postoperative period following CABG. CPK MB was present in the serum of both patients. An additional two patients had CPK MB but no QRS changes of MI. Thus, four of these seven patients (57 per cent) had CPK MB detected postoperatively. The three remaining patients had neither QRS change nor CPK MB appearance.

None of the 65 patients who returned for restudy sustained myocardial infarction or died as a result of catheterization.

Nine of the 65 patients (14 per cent) had QRS changes diagnostic of myocardial infarction in the immediate postoperative period. All eight of these patients who had postoperative CPK isoenzyme determinations had CPK MB present. The duration of CPK MB in the serum in these patients ranged from 6 to 42 hours (Table I). Peak quantitative CPK MB ranged from less than 50 to 456 units (Table II). An additional 21 patients (32 per cent) had serum CPK MB postoperatively in the absence of ECG QRS changes indicative of infarction. Nineteen of these had serial ST and/or T wave changes; however, two had persistent absence of any ECG change. The duration of CPK MB also ranged from 6 to 42 hours (Table I). Peak quantitative CPK MB in these 21 patients ranged from less than 50 to 536 units (Table II). A total of 29 patients (45 per cent) had CPK MB following surgery. There was no dura

Table I. Postoperative duration of CPK MB

	6 hr	18 hr	36 hr	42 hr
Pos. ECG, pos. CPK MB (8)*	38% (3)‡	25% (2)	0	25% (2)
Neg. ECG, pos. CPK MB† (21)	52% (11)	29% (6)	10% (2)	5% (1)

*One patient had CPK MB on the fourth and fifth postoperative days only.
†One patient had CPK MB on the evening of surgery and then again 3 days later.
‡Parentheses indicate number of patients.

Table II. Postoperative quantitative CPK MB

	< 100*	100-199*	200-299	> 300
Pos. ECG, pos. CPK MB (8)	25% (2)	25% (2)	13% (1)	38% (3)
Neg. ECG, pos. CPK MB (21)	62% (13)	14% (3)	19% (4)	5% (1)

*International Units of CPK MB per liter.

Table III. Anginal status in diagnostic subgroups

	Functional Class I for angina or improved 2 functional classes	
Neg. CPK MB, neg. ECG (35)	71%	(25)
Pos. CPK MB, neg. ECG (21)	71%	(15)
Pos. CPK MB, pos. ECG (8)	75%	(6)

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*One patient had CPK MB on the fourth and fifth postoperative days only

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‡Parentheses indicate number of patients.

Table II Postoperative quantitative CPK MB

	*< 100**	*100-199*	*200-299*	*> 300**
Pos ECG pos CPK MB (8)	25% (2)	25% (2)	13% (1)	38% (3)
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Pos CPK MB neg ECG (21)	71%	(15)
Pos CPK MB pos ECG (8)	75%	(6)

Table IV ECG (QRS changes) sensitivity and specificity

Ventriculogram	ECG +	ECG−
New apical abnormality (29 patients)	21% (6)	79% (23)
New apical plus other abnormality (7 patients)	14% (1)	86% (6)
New other abnormality (4 patients)	25% (1)	75% (3)
No new abnormality (22 patients)	0%	100% (22)

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tion or peak level of CPK MB which reliably separated those with both CPK MB and QRS changes of MI from those with CPK MB alone The remaining group of 35 patients (55 per cent) had no CPK MB detected after surgery Twenty eight of these had serial ST and/or T wave changes

Myocardial infarction following the perioperative period was documented in only one of the 65 patients Symptoms of heart failure were present in only one of the 65 patients prior to surgery and did not appear in any additional patients by the 1 year evaluation One year after surgery 38 patients (58 per cent) had improved to functional Class I for angina and an additional 10 patients (15 per cent) had improved two functional classes (i e from Class IV to Class II) An analysis of the postoperative enzyme and ECG data (Table III) revealed similar improvement of angina in those with and without evidence of perioperative myocardial infarction

Of the 28 patients with adequate treadmill exercise tests before and after surgery 21 were initially positive Fourteen of these became negative postoperatively All seven who were initially negative remained negative after coronary artery bypass grafting Among patients who had positive preoperative tests those with and without postoperative CPK MB had a similar incidence (69 and 60 per cent) of conversion to negative at the 1 year evaluation

Hemodynamic data were available for all 65 patients from both cardiac catheterizations Changes in arteriovenous oxygen difference cardiac index and left ventricular end diastolic pressure were analyzed When the mean values of each of these were compared from the two catheterizations no significant change was found

Differences between pre and 1 year postoperative hemodynamic parameters were compared among three groups of patients those with CPK MB and QRS changes those with CPK MB alone and those with neither of these No significant difference could be found among these three groups

Another descriptor of perioperative infarction new asynergy was analyzed Only the RAO projection was considered since there were no patients in whom interim contraction abnormalities were seen only on the LAO view Sixty three of 65 patients had pre and postoperative left ventricular cineangiograms that were adequate for comparative analysis One additional patient who had a documented myocardial infarction after the perioperative period was excluded Of the remaining 62 patients 31 (50 per cent) had ventricular asynergy preoperatively One year after surgery three of these (10 per cent) had an improved contraction pattern

Forty patients (65 per cent) had new areas of asynergy Twenty nine of these (73 per cent) were confined to the apex, seven (18 per cent) involved both apical and nonapical sectors and four (10 per cent) were confined to basal and middle sectors Twenty seven of the 29 patients with new isolated apical asynergy had been vented through the apex Thus the vent site was the most common location of new asynergy but only 34 of the patients (58 per cent) who had an apical vent developed a new apical abnormality Also two patients without apical vents had new apical asynergy Two thirds of the new apical abnormalities were dyskinetic areas (bulging paradoxically during systole) There were no angiographic features which distinguished apical abnormalities present in the preoperative studies or those seen postoperatively in nonvented patients from those observed in patients who had apical vents Thus it was impossible to determine the true incidence of new asynergy which was not caused by the intraoperative procedure of apical venting

Thirteen (21 per cent) of the patients restudied had new asynergy that could not be attributed to a left ventricular vent This group included 11 patients with new nonapical asynergy and two patients with new apical asynergy who had not had a left ventricular vent These 13 patients formed a subgroup in which myocardial infarction was most likely and they were therefore compared with those least likely to have had

Table V Ventriculographic and vascular changes in patients with QRS changes on ECG

Patient	ECG location interim MI	Bypass grafts inserted	Bypass grafts occluded	Interim distal progressive native disease	Site interim akin.-dyskin	Possible etiologic occlusion
R S	Ant†	LAD	—	—	Apex	None
T C	Ant	LAD R	R	LAD	Uninterpretable due to PVCs	Graft, native
R N	Ant	LAD R C	LAD	LAD	Apex	Graft native
G B	Ant Lat Inf	LAD	LAD	LAD	Apex	Graft native
G S	Ant	LAD R	LAD	—	Ant	Graft
V C	Lat	LAD C	—	—	Apex	None
E S	Ant	LAD R C	—	—	Apex	None
E D	Ant Inf	LAD R	—	LAD	Apex	Native
D W	Inf	LAD R	—	—	Apex	None
A G	Inf	LAD	—	R-C	Ant Inf	Native

*Acute MI following the immediate postoperative period
†Abbreviation Ant = anterior Lat = lateral Inf = inferior LAD = left anterior descending R = right C = circumflex PVC's = premature ventricular contractions.

infarction the 22 patients who had no new asynergy Ten of the 13 (77 per cent) with new asynergy had improved to functional Class I or improved two classes compared to 14 of 22 (64 per cent) of those without new asynergy This was not a statistically significant difference ($p > 0.05$)

The incidence of postoperative QRS change and CPK MB was determined in the 13 patients (21 per cent) who had new asynergy that could not be attributed to a left ventricular apical vent Only two of the 13 patients had QRS changes and an additional five had CPK MB detected Thus 46 per cent of this group with asynergy (six of 13) had neither perioperative nor subsequent documentation of myocardial infarction

The sensitivity and specificity of ECG and QRS changes of infarction are shown in Table IV When the ECG was indicative of infarction new asynergy was always observed However 32 of the 40 patients with new asynergy (80 per cent) had no QRS changes on the ECG ECG QRS changes of infarction were therefore 100 per cent specific for new asynergy but only 20 per cent sensitive The site of asynergy was apical in six of the eight patients with diagnostic QRS changes The ninth patient with QRS changes indicating infarction on ECG had multiple premature beats on the postoperative ventriculogram which precluded interpretation

The relationships between ECG location of infarction and ventriculographic site of contraction abnormality are shown in Table V Anterior location on the ECG was frequently observed when the interim contraction abnormality was limited to the apex Despite grafting of the left anterior descending coronary seven of the nine had QRS changes which were apparent in anterior leads (V_1 to V_3) In two of these the graft was occluded and in three others there was progression of disease in the native circulation at or distal to the graftsite during the interim year

Table VI CPK MB sensitivity and specificity

Ventriculogram	+ CPK MB	+ CPK MB > 18 hr
New apical abnormality (28 patients†)	50% (14)	32% (9)
New apical plus other abnormality (7 patients)	71% (5)	43% (3)
New other abnormality (4 patients)	50% (2)	25% (1)
No new abnormality (27 patients)	22% (6)	11% (3)

+ CPK MB 78 per cent specific for ventriculographic abnormality (21/27 patients) 64 per cent sensitive for nonapical change 50 per cent sensitive for apical change alone Using + CPK MB > 18 hr 87 per cent specific (13/15 patients) but only 33 per cent sensitive (13/39 patients) for apical and nonapical changes.
*One patient excluded because of interim MI
†One patient excluded who did not have enzymes drawn

CPK MB sensitivity and specificity are shown in Table VI When CPK MB was present new asynergy was observed in 78 per cent of patients However 18 of the 39 patients with new asynergy (46 per cent) had no CPK MB detected The presence of CPK MB was therefore 78 per cent specific but only 54 per cent sensitive for new asynergy

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Differences between pre and 1 year postoperative hemodynamic parameters were compared among three groups of patients those with CPK MB and QRS changes those with CPK MB alone and those with neither of these No significant difference could be found among these three groups

Another descriptor of perioperative infarction new asynergy, was analyzed Only the RAO projection was considered since there were no patients in whom interim contraction abnormalities were seen only on the LAO view Sixty three of 65 patients had pre and postoperative left ventricular cineangiograms that were adequate for comparative analysis One additional patient who had a documented myocardial infarction after the perioperative period was excluded Of the remaining 62 patients 31 (50 per cent) had left ventricular asynergy preoperatively One year after surgery, three of these (10 per cent) had an improved contraction pattern

Forty patients (65 per cent) had new areas of asynergy Twenty nine of these (73 per cent) were confined to the apex seven (18 per cent) involved both apical and nonapical sectors, and four (10 per cent) were confined to basal and middle sectors Twenty seven of the 29 patients with new isolated apical asynergy had been vented through the apex Thus the vent site was the most common location of new asynergy, but only 34 of the patients (58 per cent) who had an apical vent developed a new apical abnormality Also two patients without apical vents had new apical asynergy Two thirds of the new apical abnormalities were dyskinetic areas (bulging paradoxically during systole) There were no angiographic features which distinguished apical abnormalities present in the preoperative studies or those seen postoperatively in nonvented patients from those observed in patients who had apical vents Thus it was impossible to determine the true incidence of new asynergy which was not caused by the intraoperative procedure of apical venting

Thirteen (21 per cent) of the patients restudied had new asynergy that could not be attributed to a left ventricular vent This group included 11 patients with new nonapical asynergy and two patients with new apical asynergy who had not had a left ventricular vent These 13 patients formed a subgroup in which myocardial infarction was most likely and they were therefore compared with those least likely to have had

ot known Similarly it is not known precisely ow much myocardial necrosis can occur before synergy will be seen on the ventriculogram Five f these six patients had asynergy on the preoperative ventriculogram and it would be expected hat the cineangiographic detection of new asynergy might be more difficult in this group

Therefore QRS changes as descriptors of perioperative infarction are limited in their sensitivity or new asynergy and CPK MB is limited in its sensitivity and specificity for new asynergy However asynergy also needs to be examined more closely as a descriptor of perioperative infarction Myocardial infarction as a cause of asynergy may have occurred at any time prior to the second catheterization Although only one patient was found to have had a documented MI after the perioperative period (and excluded from ventriculographic analysis) subsequent infarction may have occurred and been masked by pain related to surgery or by previous ECG abnormalities QRS changes were present in 30 per cent of the restudy patients preoperatively and in 43 per cent after the perioperative period New asynergy therefore may not have been related in all patients to perioperative infarction but may have been due to a subsequent unrecognized MI Furthermore asynergy may not always represent infarction Transient wall motion abnormalities due to ischemia have been reported[2] Postoperative epicarditis and/or pericarditis and mediastinal adhesions might also theoretically alter the cineangiographic contraction pattern The majority of patients with new asynergy in this study had apical abnormalities presumed due to the left ventricular vent Seventy five per cent of patients with ECG QRS changes and 45 per cent of patients with CPK MB had left ventricular apical vents and asynergy confined to the apex Therefore the incidence of perioperative infarction unrelated to the apical vent cannot be determined from this study There were no ECG and/or CPK MB descriptors which separated patients with new apical asynergy from those with non apical changes

This study found no relationship between descriptors of myocardial infarction and pain relief Analysis of the pre and 1 year postoperative coronary arteriograms has been performed in these patients Symptomatic improvement was significantly correlated with patency of the native and grafted vessels suggesting that this parameter rather than infarction is the major determinant of postoperative pain relief

ECG QRS changes were found to be specific but insensitive predictors of new asynergy CPK MB was more sensitive but less specific Patients having one or both of these descriptors of perioperative infarction were not significantly different from the remainder of the study population with respect to subsequent death development of heart failure conversion of the treadmill from positive to negative or hemodynamic changes at 1 year

This study documents the course of 103 consecutive patients during the first year following coronary artery bypass surgery The incidence of presence of ECG isoenzymatic and ventriculographic parameters suggestive of myocardial infarction is high but the mortality and morbidity rates following initial hospital discharge are quite low A study is now in progress to determine the relationship between intraoperative manipulations and CPK MB release and studies are planned for the return of patients who did not have a left ventricular apical vent to correlate their perioperative descriptors of acute myocardial infarction and their subsequent clinical course and ventriculographic appearance

Summary

The incidence of ECG (14 per cent) indication of acute myocardial infarction complicating coronary artery bypass surgery is documented corroborating the findings of prior series An additional 32 per cent of patients had appearance of myocardial specific CPK MB in serum during the immediate postoperative period All patients surviving to 1 year following surgery (93 of 103) were asked to return for repeat cardiac catheterization to determine the presence and extent of interim ventricular contraction abnormalities Sixty five (70 per cent) of the group returned for evaluation Preoperative and 1 year postoperative left ventriculograms were compared to determine if new contraction abnormalities would confirm the specificity of perioperative QRS and isoenzyme changes and if the absence of new abnormalities would confirm their sensitivity The majority of patients (65 per cent) had new areas of asynergy However 73 per cent of these were confined to the apex and thus could have been produced by the vent employed during cardiopulmonary bypass QRS changes were 100 per cent

Further analysis of the quantity and duration of CPK MB was performed in an attempt to increase specificity without significant loss of sensitivity When CPK MB was detected for more than 18 hours postoperatively, the specificity for new asynergy increased from 81 to 87 per cent, the sensitivity was reduced for both apical and nonapical changes Similarly, use of the peak quantitative CPK MB value was of no additional benefit in increasing specificity while maintaining sensitivity for new asynergy

The specificity of CPK MB with and without concurrent QRS change was then examined CPK MB when associated with QRS change was 100 per cent specific for new asynergy, but only 70 per cent specific if present without QRS change When neither QRS change occurred nor CPK MB was detected new asynergy was present 53 per cent of the time (18 of 34) A statistically significant difference ($p < 0.01$) was present only between those with both QRS changes and CPK MB and those with neither The percentage of patients in whom asynergy may have been due to the apical vent was similar (71 64 and 67 per cent, respectively) in each of these three groups

Discussion

QRS changes, other than conduction disturbances, are specific but relatively insensitive indicators of myocardial infarction being absent in 30 per cent of autopsy proved cases of infarction[17] and absent in roughly the same percentage of patients with MI diagnosed by combined ECG and isoenzyme analysis[19] Of the 40 patients in this study with new asynergy only 20 per cent had QRS changes indicative of infarction The incidence was 15 per cent in the 13 patients in whom new asynergy could not have been caused by the left ventricular apical vent This emphasizes the need for enzyme analysis to increase the capability for diagnosing perioperative infarction

CPK MB has been reported to be 100 per cent sensitive and 99 per cent specific for acute myocardial infarction in the setting of a coronary care unit,[19] and to be a reliable index of myocardial damage following coronary artery bypass grafting and other surgical procedures Although skeletal muscle contains a small amount of CPK MB in addition to the usual CPK MM form, serum CPK MB has been absent with massive skeletal muscle injury and elevation of the total CPK as high as 104 000 I U /L

Accurate assessment of post bypass incidence of myocardial infarction has been quite difficult because of hemolysis from transfused blood elevating SGOT, LDH and LDH isoenzymes and intraoperative skeletal muscle trauma elevating SGOT, total LDH, and total CPK Postoperative hepatic and pulmonary dysfunction when present, are other sources of falsely elevated SGOT and LDH values ST and T wave changes have been of little help because of the high frequency of postoperative pericarditis and of perioperative myocardial ischemia

Forty five per cent of the patients in this study had CPK MB detected during the immediate postoperative period This finding is similar to that reported by Dixon and associates who found presence of CPK MB in 51 per cent of patients following coronary artery bypass grafting

ECG QRS changes alone while specific, were inadequate indicators of infarction because 80 per cent of the patients who developed new asynergy had no new QRS changes Forty six per cent of patients with new asynergy had neither QRS changes nor CPK MB detected The sensitivity of CPK MB for new asynergy may have been greater had intraoperative and immediate postoperative sampling been done This is suggested by the study of Oldham and associates, who found a higher incidence of CPK MB (76 per cent) in patients who had intraoperative in addition to postoperative sampling, with CPK MB being detected for as short a period as 1 4 hours in some patients As sampled in this study therefore CPK MB may not be as sensitive an indicator of myocardial damage as it potentially could be with sampling done earlier than 6 hours postoperatively

The extent to which the presence of CPK MB after coronary artery bypass grafting indicates myocardial necrosis is not known While the specificity of QRS changes for new asynergy was 100 per cent the specificity of CPK MB without QRS changes was only 70 per cent In the patients (30 per cent) who had postoperative CPK MB but no new asynergy we may assume that perioperative necrosis occurred but was not sufficient to result in asynergy as revealed by the ventriculogram The extent of myocardial damage necessary to detect CPK MB in the serum is

The effect of propranolol on hemolysis in patients with an aortic prosthetic valve

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The occurrence of hemolytic anemia from prosthetic material within the heart has been well documented[1] and has been reported most often in patients with prosthetic aortic valves These individuals usually respond well to iron replacement and decreased physical activity However an occasional patient will have severe hemolysis which is refractory to medical management and which may be controlled only by reoperation It was postulated that propranolol by slowing the heart rate and decreasing the rate of ejection might decrease turbulence and thereby decrease hemolysis We present data on the use of propranolol in five patients with severe hemolysis

Methods

Each patient had a hematocrit below 30 vol per cent at low levels of physical activity prior to the study while taking the maximum tolerated dose of iron and 5 mg of folic acid each day The iron and folic acid were continued at the same dosage throughout the study The patients had received this treatment for at least 1 month before entering the study All patients were in normal sinus rhythm Patients were admitted to the Clinical Research Unit of the University of Michigan Center for these studies Informed consent was obtained from all patients The exercise level was kept as constant as possible with the use of a pedometer to measure the distance walked each day during the three phases of the study In addition a 4 minute period of stationary bicycle exercise at a speed of 10 miles per hour (mph) with a constant resistance setting was carried out daily with the heart rate recorded before and after exercise

Red cell survival studies were carried out during the stay in the Clinical Research Unit by the chromium 51 half life method (normal 26 to 30 days) Daily hematocrit (Hmct) hemoglobin (Hgb) reticulocyte count serum hemoglobin and serum lactic dehydrogenase (LDH) levels were obtained In addition there was a daily 24 hour urine collection for creatinine protein hemoglobin and free iron determinations Urine iron was measured by the tripyridyl triazine method Chest x ray and electrocardiogram were obtained to monitor rhythm and heart size during the three phases of the study Serum iron total iron binding capacity platelet count complete blood count with peripheral smear serum creatinine serum glutamic oxalacetic transaminase LDH isoenzyme electrophoresis stool guaiac and urine analysis were obtained at the time of each admission to exclude evidence of blood loss or evidence of other medical conditions such as hepatitis A Coombs test was obtained during each phase of the study to exclude other reasons for hemolysis

After the baseline evaluation patients were given propranolol daily in the following amounts Patient 1 and 4 80 mg Patient 2 20 mg Patients 3 and 5 40 mg These were the largest doses that it was felt the patient could tolerate

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specific and CPK MB appearance was 78 per cent specific but they were only 20 and 54 per cent sensitive, respectively Indeed 46 per cent of those with new asynergy which was non apical had neither QRS change nor CPK MB appearance Thus QRS changes were always—and CPK MB appearance was usually—associated with new asynergy but, in addition, many patients with no perioperative indication of infarction developed new areas of left ventricular contraction abnormality within the first postoperative year

REFERENCES

1 Keelan M H Tresch D D Co E H et al Incidence mortality rate and sequelae of myocardial infarction immediately after coronary artery bypass surgery J Lab Clin Med 78 802 1971
2. Greenberg B McAllister B Frye R and Wallace B Serum glutamic oxalate transferase and electrocardiographic changes after myocardial revascularization procedures in patients with coronary artery disease Am J Cardiol 26 135 1970
3 Dietrich E Liddicoat J Alessi F et al Serum enzyme and electrocardiographic changes immediately following myocardial revascularization Ann Thorac Surg 5 195 1968
4 Morris G C Reul G J Howell J F et al Follow up results of distal coronary artery bypass for ischemic heart disease Am J Cardiol 29 180 1972
5 Hallin R W Page U S Bigelow J C et al Revascularization of the heart aortocoronary bypass in sixty three patients Am J Surg 122 164 1971
6 Hultgren H N Miyagawa M Buck W et al Ischemic myocardial injury during coronary artery surgery Am Heart J 82 624 1971
7 McNeer J F Wagner G S Brewer D L and Rosati R. A Immediate and long term risk of perioperative infarction Experience with 447 consecutive patients Manuscript in preparation
8 Oldham H N Roe C R Young W G et al Intraoperative detection of myocardial damage during coronary artery surgery by plasma creatine phosph[illegible] nase isoenzyme analysis Surgery 74 91[illegible] 19[illegible]
9 Dixon S H Limbird L E Roe C R Wagner G [illegible] al Recognition of postoperative acute myocard[illegible] infarction Circulation 47-48(Suppl 3) 13[illegible] 19[illegible]
10 Wagner G S Roe C R Limbird L E et al [illegible] importance of identification of the myocardial [illegible] isoenzyme of creatine phosphokinase (MB form) [illegible] diagnosis of acute myocardial infarction Circul[illegible] 47 263 1973
11 Bruce R A and Hornstein T R Exercise stress te[illegible] in the evaluation of patients with ischemia heart d[illegible] Prog Cardiovasc Dis 11 371 1969
12 Rose G A and Blackburn H Cardiovascular su[illegible] methods, World Health Organization Monograph [illegible] No 56 Geneva 1968
13 Rosalki, S B An improved procedure for serum cre[illegible] phosphokinase determination J Lab Clin Med. 69 [illegible] 1967
14 Roe C R Limbird L E Wagner G S and Nerenb[illegible] S T Combined isoenzyme analysis in the diagnos[illegible] myocardial injury Application of electrophoretic me[illegible] ods for the detection and quantitation of the CPK [illegible] isoenzyme J Lab Clin Med 80 577 197[illegible]
15 Herman M V Heinle R A Klein M D and Go[illegible] R. Localized disorders in myocardial contraction [illegible] Engl J Med 277 222 1967
16 The Criteria Committee of the New York Heart Asso[illegible] tion Nomenclature and criteria for diagnosis of di[illegible] of the heart and great vessels ed 7 Boston 1973 L[illegible] Brown & Company
17 Johnson W J Achor R W P Burchell H B [illegible] Edwards, J E Unrecognized myocardial infarc[illegible] Arch Intern Med 103 253 19[illegible]9
18 Roe C R Unpublished observation
19 Dixon S H Fuchs J C A and Ebert P A Change[illegible] serum creatine phosphokinase activity following th[illegible] ic cardiac and abdominal operations Arch Su[illegible] 103 66 1971
20 Banka Y S Bodenheimer M and Helfant R [illegible] Determinants of reversible asynergy Circulation 5[illegible] 1974
21 Hartman C W Kong Y Margolis J R Warren, [illegible] Peter R A and Behar V S Aortocoronary b[illegible] surgery Angiographic and functional correlation at [illegible] year Am J Cardiol (in press)

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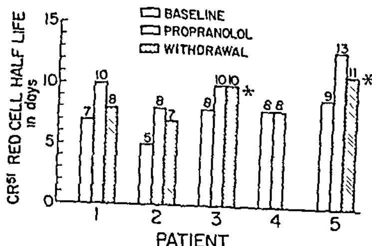


Fig 1 Red cell survival for the three study periods Propranolol was not continued between the propranolol and propranolol withdrawal study

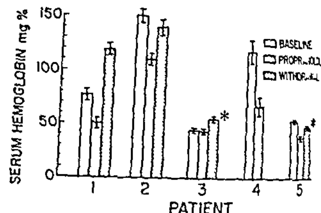


Fig 3 Serum hemoglobin values (mean and standard deviation) for the three study periods Propranolol was not continued between the propranolol and propranolol withdrawal study

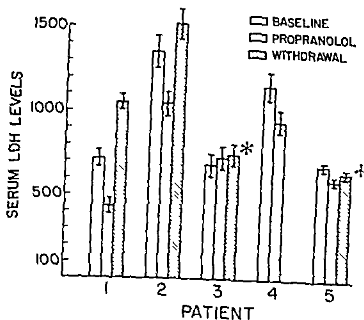


Fig 2 Serum LDH values (mean and standard deviation) for the three study periods Propranolol was not continued between the propranolol and propranolol withdrawal study

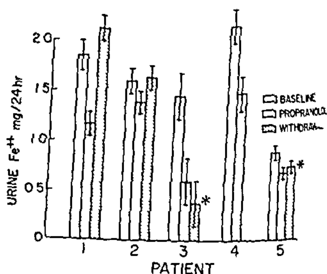


Fig 4 The 24 hour urine iron values (mean and standard deviation) for the three study periods Propranolol was not continued between the propranolol and propranolol withdrawal study

and still cause a drop in exercise heart rate Each patient was readmitted 1 month later and had the above studies repeated while receiving propranolol One month later they were again readmitted and studied after propranolol therapy was discontinued for 48 hours Patients 3 and 5 did not continue propranolol therapy between the second and third evaluations, Patients 1 2 and 4 did continue this treatment Patient 4 left our geographic area and therefore did not have the propranolol withdrawal study

The mean and standard error of the mean of the daily laboratory values for each part of the study are given in the tables Each patient serves as his own control in that comparisons are made within patients under the three different conditions The means of the daily LDH values serum hemoglobins 24 hour urine excretion levels and postexercise heart rates were compared for differences among the three study periods by Scheffe's' method of multiple comparisons following the analysis of variance

Results

Fig 1 displays the red cell half life survival times for the three study periods Patients 1 2 3 and 5 demonstrated an increase in red cell survival times with propranolol therapy However only patients 1 2 and 5 showed a decrease in red cell survival after propranolol withdrawal

[Tab]le I Changes in mean LDH, serum hemoglo[bin,] and urine iron excretion with propranolol [the]rapy

[P]atient		LDH (IU)		S Hgb (mg/100 ml)		U Fe (mg/24 hr)	
	B	718	(45)±	7	(6.5)	1.85	(0.16)
	P	435	(41)	51	(5.6)	1.85	(0.13)
	W	1,061	(45)	119	(5.9)	2.13	(0.14)
	B	1,354	(91)	151	(6.5)	1.60	(0.14
	P	1,055	(80)	111	(5.7)	1.39	(0.12)
	W	1,5?0	(91)	141	(7.0)	1.64	(0.13)
	B	698	(65)	45	(2.7)	1.45	(0.23)
	P	428	(72)	44	(2.7)	0.57	(0.23)
	W	753	(68)	5?	(2.8)	0.3	(0.23)
	B	1,1??	(88)	1?2	(11.?)	2.15	(0.17)
	P	949	(6?)	68	(9)	1.4	(0.15)
	W	—	—	—	—	—	—
	B	69?	(20)	54	(1.6)	0.89	(0.0)
	P	609	(?0)	38	(1.5)	0.68	(0.06)
	W	659	(19)	47	(1.3)	0.73	(0.06)

[B] Baseline; P, propranolol therapy; W, propranolol withdrawal.
[±] standard error of the m[ea]n.

The mean red cell half life for the five patients was 7.4 days at baseline, 9.8 days during propranolol therapy, and 8.6 days after propranolol withdrawal. The cell survival may have a ± 15% variation in values with *repeat testing*. Therefore, this change is greater than expected by variation of the method.

Fig. 2 and Table I give the mean LDH values with the standard error of the mean. The analysis of variance for the values *obtained* during each study period showed that patients 1 and 5 had a significant reduction in LDH between the baseline and the propranolol treatment periods ($p < 0.05$). Patients 1 and 2 had significant increases in LDH between the *propranolol* treatment period and the withdrawal period ($p < 0.05$). The serum hemoglobin values are displayed in Fig. 3 and in Table I. Patients 2, 4, and 5 had a significant drop in the serum hemoglobin values with the propranolol treatment period ($p < 0.05$). Patients 1, 2, and 5 showed significant increases *in serum* hemoglobin between the propranolol treatment and withdrawal periods ($p < 0.05$). Fig. 4 and Table I give the mean 24 hour urine iron excretion values

Table II Heart rate after exercise

Patient	Baseline		Propranolol		Withdrawal	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
1	125	(?8)	99	(?6)	115	(2.6)
2	119	(3.5)	95	(3.5)	101	(3.7)
3	144	(?4)	1?4	(2.4)	140	(2.8)
4	103	(?8)	94	(3.2)	—	—
5	9?	(2.5)	79	(3.3)	97	(2.5)

Propranolol was not continued between the propranolol and propranolol withdrawal study.

Table III Mean of the daily hematocrits (H) in volumes per cent and mean reticulocyte counts (R) for the three study periods

Patient		Baseline	Propranolol	Withdrawal
1	H	26	29	26
	R	11	7	11
2	H	24	29	27
	R	14	10	13
3	H	31	34	33
	R	10	7	8
4	H	2	?8	
	R	18	1?	
5	H	30	3?	3?
	R	9	8	10

Propranolol was not continued between the propranolol and propranolol withdrawal study.

According to Scheffe's method of multiple comparisons for the analysis of variance, Patients 3 and 4 had a significant drop in iron excretion for the baseline value in comparison to the propranolol treatment period ($p < 0.05$). Only Patient 1 had a significant increase ($p < 0.05$) in iron excretion after propranolol withdrawal. The exercise heart rates for the three study periods are shown in Table II. Patients 1, 2, 3, and 5 showed a *significant* drop in heart rate with propranolol therapy ($p < 0.05$). Patients 1, 3, and 5 had a *significant* increase in heart rate after propranolol withdrawal ($p < 0.05$).

The values for the 24 hour urine hemoglobin for the baseline, propranolol treatment, and propranolol withdrawal periods for Patient 1 were 1 321, 233, and 3 202 mg per 24 hours, respectively. The values for Patient 2 were 1 710, 48, and 602 mg per 24 hours, respectively. The other patients did not excrete adequate hemoglobin for measurement. The mean hematocrits and reticulocyte counts for the three study periods are listed in

Table IV Response to propranolol withdrawal in Patient 1

	Day 1	2	3	4	5	6	7	8
Hematocrit (vol %)	28 7	30 7	26 2	26 8	26 2	24 6	23 6	2[illegible]
LDH(I U)		970	870	910	1 570	900	960	1130
Serum hemoglobin (mg /100 ml)	91	106	95	108	105	165	116	1[illegible]
Urine hemoglobin (mg /24 hr)	1 695	2 536	2 468	2 477	3 531	4 245	4 [illegible]	3 [illegible]
Urine iron (mg /24 hr)	1 95	2 38	1 77	1 88	1 31	3 1	2 45	[illegible]

Table V Cardiac catheterization data

Patient	Aortic leakage	Transvalvular gradient (mm Hg)
1	+	40
2	0	36
3	0	0
5	+	35

+ = mild ++ = moderate +++ = marked

Table III The increase in hematocrit during the propranolol treatment was modest in Patients 1 2, and 3 while the mean reticulocyte values dropped in these three patients Patient 1 did have a dramatic response to propranolol withdrawal, as can be seen from Table IV Reinstitution of propranolol therapy and rest were effective in controlling the hemolytic crisis

Table V lists the findings in the four patients who had cardiac catheterization Patients 1 2 and 5 each had an important aortic transvalvular pressure gradient no patient had serious paravalvular leakage

Discussion

Hemolytic anemia secondary to prosthetic heart valves was noted infrequently with the early non-cloth covered valves[4] In an effort to decrease thromboembolism the Starr Edwards Laboratories developed the totally cloth covered aortic valve prosthesis Patients with these valves were noted to have an increase in hemolysis and subsequent anemia[8] In a majority of patients this anemia responds to oral iron therapy Rarely however, it is necessary to replace the prosthetic valve

There are a number of mechanisms by which hemolysis may be produced by a prosthetic aortic valve First paravalvular leakage may cause hemolysis[10] Second the type of material of which the valve is made may play a part in red cell destruction Third the turbulence caused by a transvalvular gradient may cause red cell destruction through shearing forces on the red cells[11] Finally, wearing of the cloth on the struts may expose the red cells to surfaces with undesirable characteristics and lead to an increase in red cell breakdown[11 14] We postulate that propranolol by producing a decrease in heart rate with less frequent seating of the ball should decrease the mechanical trauma to the red cells and by slowing the rate of ejection of blood into the aorta would result in decreased turbulence The decrease in exercise heart rates while on propranolol would suggest that this could indeed be an explanation for the decrease in hemolysis Perhaps the propranolol should have been withdrawn for a longer time before the withdrawal studies since our heart rates were generally lower than the baseline values for the withdrawal period Unfortunately we did not obtain left ventricular ejection times during the study to document this possible mechanism If paravalvular leakage is the major reason for hemolysis propranolol by slowing the heart rate might worsen the hemolysis These patients would however be excluded from the use of propranolol on a hemodynamic basis

Patient 1 had an increase in red cell half life and an expected drop in serum LDH serum hemoglobin, and urinary iron excretion The exercise heart rate was slowed by the propranolol therapy Propranolol therapy was successful in forestalling reoperation and was felt to be a clinically useful addition to the therapy of this patient Patient 2 could tolerate only a small amount of propranolol however this did produce a significant decrease in exercise heart rate Red cell half life was prolonged and the other parameters suggested less hemolysis during propranolol therapy Upon withdrawal of propranolol there was an increase in LDH and serum hemoglobin

ly but the heart rate did not rise to baseline ly and the red cell half life showed little

The propranolol was felt to be helpful in abling the patient to be more active until the set of congestive failure forced the elimination this therapy. Patient 3 had little measurable crease of hemolysis with propranolol therapy d even though the hematocrit had risen the dication was stopped with no drop initially in hematocrit. Patient 4 had a disparity between e red cell half life which did not change during opranolol therapy and the serum hemoglobin lues and urine iron excretion which decreased gnificantly. The heart rate after exercise showed ly a modest drop which could reflect an adequate propranolol effect or an inadequate ork load. The patient was convinced of the nefit of propranolol therapy. However when e study was repeated off propranolol 2 years ter the serum LDH hemoglobin and iron excretion levels were decreased and the red cell half life as unchanged. Therefore we could not confirm a enefit propranolol treatment. Patient 5 had creased red cell half life with propranolol herap and significant decrease of serum LDH nd hemoglobin values. Heart rate slowing was oted with propranolol. The patient felt fatigued hile taking propranolol and it was discontinued as she was able to maintain a satisfactory hematocrit level without this agent. The clinical usefulness of propranolol in the management of hemolysis is not yet clear from our experience. In selected patients with significant morbidity from the anemia no major hemodynamic dysfunction of the valve and adequate left ventricular function we will consider a trial of propranolol for palliation. Unfortunately many of these patients eventually will need replacement of the defective valve.

The hazards of propranolol therapy in patients with prosthetic valves are exemplified by Patient 2. An initial hypotensive response to propranolol was noted and then even on a small total daily dose of 20 mg a day she developed congestive heart failure after approximately 6 months. Patients with poor ventricular function or a marked mechanical defect of the valve such as obstruction or leakage have a contraindication to this form of therapy even when low doses are given. If this therapy is considered cardiac catheterization may be needed to exclude serious obstruction or leakage prior to propranolol therapy.

Summary

Propranolol was given to five patients with severe hemolytic anemia from aortic prostheses. Red cell survival lactic dehydrogenase serum hemoglobin and 24 hour urine iron values were used to evaluate the severity of hemolysis with and without propranolol treatment. Three patients had a clear decrease in the level of hemolysis with propranolol therapy. One patient developed congestive failure after 6 months on propranolol. The decrease in hemolysis is most likely related to a slower heart rate.

REFERENCES

1. Sigler A T Forman E N Zinkham W H and Neill C A. Severe intravascular hemolysis following surgical repair of endocardial cushion defects. Am J Med 35 467 1963
2. Sears D A and Crosby W H. Intravascular hemolysis due to intracardiac prosthetic devices. Am J Med 39 341 196
3. Brodeur M T H Sutherland D W Koler R D, Starr A Kimsey J A and Griswold H E. Red blood cell survival in patients with aortic valvular disease and ball valve prostheses. Circulation 32 570 1975
4. Rodgers B M. Hemolytic anemia following prosthetic valve replacements. Circulation 39 I 15 1969
5. Capps R D Batsakis J G Briere R O et al. Automated colorimetric (tetrazolium scale) assay for serum lactate dehydrogenase. Clin Chem 12 406 1966
6. Scheffe H. The analysis of variance. Philadelphia 1959 John Wiley & Sons, p
7. Wagner H N Jr. Nuclear medicine. New York 1975 H P Publishing Co Inc
8. Myhre E Dale J, and Rasmussen K. Erythrocyte destruction in different types of Starr Edwards aortic ball valves. Circulation 42 515 1970
9. Santinga J T Kirsh M M and Batsakis J T. Hemolysis in different series of the Starr Edwards aortic valve prostheses. Chest 63 905 1973
10. Kastor J A et al. Paravalvular leaks and hemolytic anemia following insertion of Starr Edwards aortic and mitral valves. J Thorac Cardiovasc Surg 56 2 9 1968
11. Williams A R Hughes D E and Nyborg W L. Hemolysis near a transversely oscillating wire. Science 169 8 1 1970
12. Hodam R, Starr A Raible D and Griswold H. Totally cloth covered prostheses. A review of two years clinical experience. Circulation 41 42(Suppl II) II-41 II 33 II 38 19 0
13. Schottenfeld M Wi heart J D Ross J K, Lincoln J C R and Ross D N. Cloth destruction and haemolysis with totally cloth covered Starr Edwards prostheses. Thorax 26 1 9 1971
14. Boruchow I B, Ramsey H W and Wheat M W. Complications following destruction of the cloth covering of a Starr Edwards aortic valve prosthesis. J Thorac Cardiovasc Surg 62 290 1971

The effects of oral propranolol, digoxin and combination therapy on the resting and exercise electrocardiogram

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Propranolol hydrochloride is widely used to produce beta adrenergic blockade in patients with ischemic chest pain arrhythmias and hyper tension and the majority of patients undergo chronic oral therapy While the effects of acute propranolol administration on the resting and exercise electrocardiogram have previously been described,[1-3] recent work from our laboratory suggests that oral therapy given over a two week period results in circulatory adjustments different from those occurring after acute administration of the drug[4] Many patients given propranolol also receive digitalis glycosides concurrently The effects of digitalis on the resting electrocardiogram are well known,[5] as is its association with 'false positive ischemic exercise electrocardiographic changes[6] To what extent the concurrent administration of both digitalis and propranolol might modify the resting and exercise electrocardiographic effects of either of these agents given singly has not however been examined Therefore, we designed a protocol to assess the effects of oral propranolol, digoxin and their combination, upon the resting and exercise electrocardiogram in both normal subjects and in patients with coronary artery disease

Methods

Subject selection Thirty individuals we studied Ten of these were normal volunte without evidence of cardiovascular disease The were six males and four females with an aver age of 46 years (range 31 to 59 years) Twe were patients with significant coronary art disease (CAD), based on the following (1) minimum of one coronary arterial obstruct lesion of at least 75 per cent luminal narrow demonstrated arteriographically, (2) a prev acute myocardial infarction diagnosed by typ history electrocardiographic changes and my cardial enzyme elevations (3) typical stre related angina pectoris and ischemic ST segme depression during treadmill exercise as defi below All twenty CAD patients satisfied at le two of these criteria except for one man who h typical angina pectoris and a positive exer test The average age of this group was 52 ye (range 33 to 66 years) and 19 of 20 were ma None of the patients had abnormal levels systemic arterial blood pressure during the st (defined as supine systolic blood pressure gre than 140 mm Hg or diastolic blood pres greater than 90 mm Hg) Nineteen of the 20 C patients reported intermittent stress rela chest pain consistent with angina pectoris du the course of the study Further details of CAD group have been presented elsewhere[4]

Experimental protocol The study consiste a ten week period divided into five two w segments All subjects were studied fasting, in basal state Each individual made six visits on the start of the study and one at the end of e two week segment All cardiac medications w

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ontinued before starting the protocol During first visit a complete physical examination s performed and a resting electrocardiogram is recorded The subjects then performed tread ll exercise using a modified Bruce protocol iey were encouraged to exercise until they had ached the maximum level of fatigue or chest un tolerable and on subsequent tests to attempt exercise to the same end point The first study as used as a familiarization procedure and the sults are not included in the data analysis At ich subsequent visit the physical examination sting electrocardiogram and treadmill exercise rotocol were repeated During the first two week gment all subjects received an oral placebo and ne results of studies obtained at the end of this eriod constituted the first set of control data During the second two week period all subjects received 40 mg of propranolol hydrochloride orally four times daily If this dose did not result n at least a ten per cent decrease in resting heart ate it was increased until such a reduction occurred This was necessary in only three ubjects all of whom were CAD patients Resting and exercise electrocardiograms were performed between two and three hours after the last dose of propranolol During the third two week segment the subjects continued to receive propranolol but in addition received digoxin 0 5 mg orally once a day Studies were performed 12 to 14 hours after the last dose of digoxin During the fourth two week segment propranolol was discontinued but the subjects continued to receive digoxin Finally for the last two week segment digoxin was discontinued and the subjects were placed on placebo once again Thus this last segment was the second control period

Resting 12 lead electrocardiograms were re corded at 25 mm /sec paper speed and analyzed with respect to the R R PR and QT intervals (the latter rate corrected according to the formula of Bazett) and lead II maximum T wave amplitude Resting ST segment changes were analyzed from the modified precordial leads obtained immediately before exercise (see be low)

During each exercise test the electrocardiogram was monitored using modified V and V precor dial leads Subjects with coronary artery disease were asked to indicate to the physician when they first noted any chest discomfort Tracings were routinely obtained immediately before exercise at 3 minute intervals during exercise at the onset of chest discomfort at the termination of exer cise and each minute thereafter for six minutes An ischemic ST segment response to exercise was defined as at least 1 mm (1 mm = 0 1 mV) of horizontal ST segment depression for at least 08 second The PR segment was used as the baseline from which the extent of ST segment change was measured

Two of the normal subjects both female had undergone cardiac catheterization for atypical chest pain and had normal intracardiac pressures left ventriculograms and coronary arteriograms In these two subjects the ST segment response to exercise was consistent with ischemia and their exercise tests therefore were classified as false positive studies For this reason only resting electrocardiographic data were used for these individuals For the other 28 subjects both resting and exercise data have been analyzed

Blood for determination of serum concentra tions of propranolol and digoxin was obtained at the appropriate visits Serum digoxin levels were determined by radioimmunoassay' and propra nolol levels by a modification of the method of Shand and associates All subjects had measur able serum digoxin and propranolol levels Mean serum digoxin concentration in the normals was 1 1 ± 08 (1 S E) ng /ml and in the CAD patients was 1 1 ± 09 ng /ml Mean serum propranolol concentration in the normals was 47 ± 9 1 ng / ml and in the CAD patients was 39 ± 6 3 ng /ml Comparison of values obtained for each of the two periods that the drugs were given did not demonstrate any significant differences

Student s t test for paired data was used for statistical analysis ' All subjects gave informed consent for participation in the study

Results

Resting electrocardiogram Resting electrocar diographic data are summarized in Table I The R R interval was significantly increased in both normals and controls during propranolol and combination therapy In normal subjects the PR interval did not change during propranolol or digoxin treatment alone but increased signifi cantly during combination therapy compared to control values In contrast CAD patients demon

$$QT\ corrected = \frac{QT\ (sec)}{\sqrt{RR\ interval\ (sec)}}$$

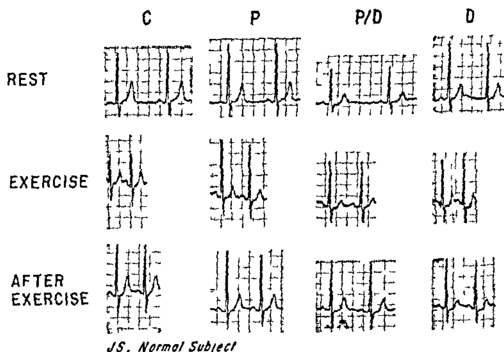


Fig 1 ECG tracings obtained at rest during exercise and after exercise in a normal subject The exercise ST segment is normal during the control and propranolol treadmill tests During combination therapy there is borderline ST segment depression and straightening With digoxin alone an ischemic response is seen with 1 to 2 mm of horizontal ST segment depression C = control P = propranolol P/D = combination therapy D = digoxin

Table I Resting electrocardiographic data in 10 normal patients and in 20 patients with CAD

	Control	*Propranolol*	*Combination*	*Digoxin*
Normals (n = 10)				
Mean R R interval (sec)	0 96 ± 0 4 (ISE)	1 11 ± 06	1 21 ± 05	0 89 ± 04
p value		p < 01	p < 001	NS
Mean PR interval (sec)	0 162 ± 004	0 165 ± 004	0 176 ± 006	0 16? ± 0?
p value		NS	p < 005	NS
Mean T amplitude (mm)	2 54 ± 39	2 70 ± 34	1 81 ± 30	1 6 ± 30
p value		NS	p < 005	p < 0
Mean QTc (sec)	0 41 ± 01	0 39 ± 01	0 36 ± 01	0 39 ± 01
p value		p < 05	p < 001	NS
CAD Patients (n = 20)				
Mean R R interval (sec)	0 91 ± 03	1 13 ± 04	1 16 ± 04	0 95 ± 04
p value		p < 001	p < 001	NS
Mean PR interval (sec)	0 161 ± 004	0 170 ± 004	0 177 ± 004	0 173 ± 004
p value		p < 001	p < 001	p < 0?
Mean T amplitude (mm)	1 75 ± 32	1 93 ± 28	1 20 ± 28	0 6? ± 3?
p value		NS	p < 02	p < 001
Mean QTc (sec)	0 40 ± 01	0 39 ± 01	0 36 ± 01	0 37 ± 01
p value		NS	p < 001	p < 001

NS = Non significant CAD = coronary artery disease
Statistical comparisons refer to study period compared to control period

strated a significant increase in PR interval as compared to control while receiving propranolol, digoxin, or their combination The small increase in PR interval on propranolol may be partially related to the observed decrease in heart rate Digoxin alone, however, did not significantly alter heart rate

In both groups lead II T wave amplitude appeared unchanged on propranolol and was significantly reduced on digoxin either alone or in combination with propranolol (Table I) The magnitude of the T wave change was somewhat greater in the CAD subjects Both propranolol and digoxin administered alone produced modest

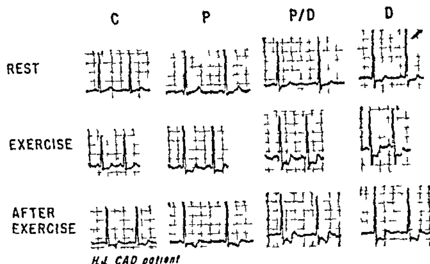


Fig. 2. ECG tracings obtained at rest, during exercise, and after exercise in a CAD patient. There is an "ischemic" control ST segment response during exercise. During propranolol therapy the ST segment is somewhat more horizontal, but the amount of depression is similar to the control study. Combination therapy results in further ST segment depression and digoxin alone in the most marked ST segment depression.

Table II. Mean exercise ST segment depression (mm) in CAD patients with ischemic control exercise tests (1 mm = 0.1 mV)

	Control	Propranolol	Combination	Digoxin
At onset of angina (n = 9)	2.2 ± 0.3 (1SE)	2.2 ± 0.4	2.4 ± 0.3	2.7 ± 0.2
p value		NS	NS	NS
Maximum ST segment depression	2.6 ± 0.3	2.5 ± 0.4	3.3 ± 0.2	3.8 ± 0.3
p value		NS	p < .00[illegible]	p < .001

CAD = coronary artery disease; NS = nonsignificant at p < .05 level.
Statistical comparisons refer to study period compared to control period.

reductions in the mean QTc in both normal subjects and CAD patients. During propranolol therapy the reduced QTc was significant only in the normal subjects and during daily digoxin only for the CAD patients. Combination therapy resulted in further shortening of the QTc which was significant for both groups.

During the second control period all of the measured variables returned to levels which were not significantly different from those observed during the first control period.

Exercise electrocardiogram

Normal subjects. None of the eight normal subjects in whom exercise tests were analyzed had ischemic ST segment changes either during the initial or final control segment of the study or while receiving propranolol alone. During digoxin administration either alone or in combination with propranolol four of these eight subjects developed an ischemic ST segment response to exercise. An example of exercise ST segment depression in a normal subject during drug therapy is shown in Fig. 1. Maximum ST segment depression in this group ranged from 2.0 to 4.0 mm on combination therapy and 2.5 to 4.0 mm on digoxin alone. However, when resting ST segment depression was subtracted from the maximum response, none of these subjects demonstrated more than 2.5 mm of maximum ST segment depression. In addition, ST segment depression was observed earlier during exercise or was greater at the same level of exercise in each of these subjects during digoxin administration alone compared to combination therapy except for one subject in whom no change was observed.

Mean maximum exercise heart rate for the normal subjects during the control period was 158 ± 4.8 beats/min. This was reduced to 123 ± 6.7 beats/min during propranolol therapy

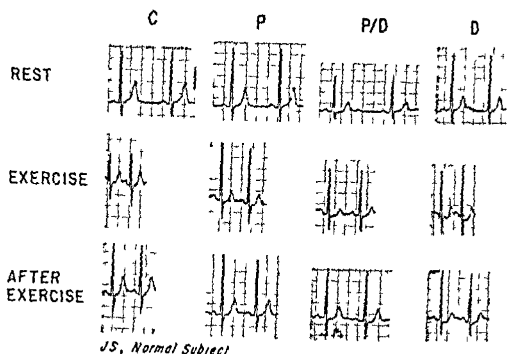


Fig 1 ECG tracings obtained at rest, during exercise and after exercise in a normal subject. The exercise ST segment is normal during the control and propranolol treadmill tests. During combination therapy there is borderline ST segment depression and straightening. With digoxin alone an ischemic response is seen with 1½ to 2 mm of horizontal ST segment depression. C = control, P = propranolol, P/D = combination therapy, D = digoxin

Table I Resting electrocardiographic data in 10 normal patients and in 20 patients with CAD

	Control	Propranolol	Combination	Digoxin
Normals (n = 10)				
Mean R R interval (sec)	0 96 ± 04 (151)	1 11 ± 06	1 21 ± 05	0 89 ± 04
p value		p < 01	p < 001	NS
Mean PR interval (sec)	0 162 ± 004	0 165 ± 004	0 176 ± 006	0 165 ± 004
p value		NS	p < 005	NS
Mean T amplitude (mm)	2 54 ± 39	2 70 ± 34	1 81 ± 30	1 76 ± 30
p value		NS	p < 005	p < 01
Mean QTc (sec)	0 41 ± 01	0 39 ± 01	0 36 ± 01	0 39 ± 01
p value		p < 05	p < 001	NS
CAD Patients (n = 20)				
Mean R R interval (sec)	0 91 ± 03	1 13 ± 04	1 16 ± 01	0 95 ± 04
p value		p < 001	p < 001	NS
Mean PR interval (sec)	0 1?1 ± 001	0 170 ± 004	0 177 ± 004	0 1?3 ± 004
p value		p < 001	p < 001	p < 005
Mean T amplitude (mm)	1 75 ± 33	1 93 ± 28	1 20 ± 28	0 64 ± 37
p value		NS	p < 02	p < 001
Mean QTc (sec)	0 40 ± 01	0 3? ± 01	0 36 ± 01	0 37 ± 01
p value		NS	p < 001	p < 01

NS = Non significant CAD = coronary artery disease
Statistical comparisons refer to study period compared to control period

strated a significant increase in *PR* interval as compared to control while receiving propranolol digoxin, or their combination. The small increase in PR interval on propranolol may be partially related to the observed decrease in heart rate. Digoxin alone however, did not significantly alter heart rate.

In both groups lead II T wave amplitude appeared unchanged *on propranolol* and was significantly reduced on digoxin either alone or in combination with propranolol (Table I). The magnitude of the T wave change was somewhat greater in the CAD subjects. Both propranolol and digoxin administered alone produced modest

der conditions approximating chronic administration In the present study two week periods of drug administration were utilized While it may be argued that this does not constitute truly chronic therapy our previous work suggests that this is sufficient time for appropriate circulatory adjustments to occur This relatively short period of time also obviates problems of disease progression in our subjects with CAD

Effects on the resting electrocardiogram Our results indicate that oral propranolol differs in its effects on atrioventricular conduction in normal subjects compared to those with CAD with the latter group exhibiting a small but significant increase in the PR interval These findings in normals are consistent with those of Stern and Eisenburg[1] who used acute intravenous propranolol but did not examine patients with heart disease While this increase was never large enough to be of concern none of our subjects had obvious underlying conduction abnormalities This observation suggests that the drug should be used with caution in patients with pre existent atrioventricular block particularly if they have coronary artery disease

In our normal subjects the addition of digoxin to propranolol resulted in significant prolongation of the PR interval which was not present while they received digoxin alone Thus in this group of normals simultaneous beta adrenergic blockade by propranolol and increased vagal tone produced by digoxin were required before significant prolongation of atrioventricular conduction was detectable on the 12 lead electrocardiogram The CAD subjects had a PR interval response which was very similar to the normal group during combination therapy However they appeared to be more susceptible than normals to prolongation of atrioventricular conduction when treated with either digoxin or propranolol alone The apparent different effects of these drugs on the PR interval of normal subjects and CAD patients could relate to abnormalities of the cardiac autonomic nervous system[3] or could be due to subclinical ischemia of the conduction system

While there appeared to be differences with respect to atrioventricular conduction time between normals and CAD patients the effects of the two drugs separately and in combination were essentially similar with respect to T wave amplitude and the QTc interval in the two groups This may be a reflection of the fact that the PR interval is determined by a number of factors including autonomic tone atrial A V nodal and infranodal conduction velocities T wave and QTc changes on the other hand might be expected to be more dependent on the direct effects of these drugs on the cellular action potential The latter effects would likely be similar in normals and CAD subjects except in areas of myocardial ischemia

Effects on the exercise electrocardiogram Previous investigators have reported that beta adrenergic blockade delays the appearance of ST segment depression during exercise testing in individuals who exhibit an ischemic response[1,2,3] and this was generally the case in our CAD patients with positive exercise tests Our results however differ from previous reports with regard to the effect of propranolol on maximal ST segment depression MacAlpin and colleagues[1] using the beta blocking agent Nethalide noted a reduction in maximum ST segment depression However these workers employed a different exercise protocol from our own keeping their subjects at a constant workload once pain occurred Russek[15] also described a reduction in maximum exercise ST segment depression after one dose of oral propranolol However in this instance a Master s two step protocol was used and the electrocardiogram may not have been recorded during the maximum increase in heart rate and systolic blood pressure Prichard and Gillam[3] attempted to quantitate the effect of propranolol on ST segment depression at the onset of angina and reported no change in their patients receiving chronic propranolol therapy Our results are in agreement with this report

Since the normal subjects and the CAD patients without an ischemia response did not show ST segment depression on propranolol it is unlikely that oral propranolol therapy has any direct effect on the ST segment If the amount of ST segment depression reflects the degree of myocardial ischemia our data in CAD patients with an ischemic exercise response suggest that the amount of ischemia required for the subjective perception of pain is unaffected by propranolol Thus if a suitably stressful exercise protocol is used patients will exercise to the same degree of ischemia whether or not they have undergone beta blockade provided they are not limited by fatigue Any fear that potentially dangerous

($p < .001$) and to 115 ± 6.9 beats/min during combination therapy ($p < .001$) During digoxin therapy, mean maximum heart rate was not significantly different from that observed during the control period

CAD patients Twelve of the 20 CAD patients (60 per cent) had ischemic ST segment depression with exercise during both control studies and eight did not show an ischemic response These two groups will be considered separately

Ischemic control exercise response Exercise ST segment changes for this group are summarized in Table II and an example of serial exercise studies in one of these patients is presented in Fig 2 All of these 12 patients had pain consistent with myocardial ischemia during control exercise studies In nine of these patients the onset of chest pain was sufficiently abrupt so that a definite time of onset could be identified

Propranolol therapy in general delayed the appearance of ST segment abnormalities during exercise but did not significantly change the amount of ST segment depression at onset of pain or maximum ST segment depression in the entire group Mean maximum exercise heart rate during the control period in these patients was 129 ± 7.4 beats/min During propranolol therapy this value was reduced to 104 ± 5.1 beats/min ($p < .001$)

Combination therapy as compared to control or propranolol therapy usually produced an earlier appearance of ST segment depression during exercise and a greater amount of ST segment depression during exercise and at the onset of angina Moreover mean maximum ST segment depression during combination therapy significantly exceeded the value obtained during the control or propranolol periods

Digoxin therapy alone resulted in resting ST segment depression ranging from 1/2 to 1 1/2 mm in seven of these 12 patients ST segment depression at the onset of angina was greater in seven of nine subjects but the mean change in ST segment depression (Table II) did not attain statistical significance Mean maximum ST segment depression however increased significantly during digoxin therapy This change was significant compared either to the control value or the value obtained during combination therapy During digoxin therapy alone the maximum exercise heart rate of 120 ± 7.3 beats/min was increased compared to the value observed during combination therapy

During the final control period all exe electrocardiograms returned to the basel observed during the first control period

Non ischemic control exercise response E of the 20 CAD subjects did not demonstrate a ischemic ST segment response to exercise dur either control study Three of these patie showed an ischemic exercise ST segment respon during combination therapy (range 1 to 3 m and during digoxin treatment alone (range 1 t 3[1] mm) Two of these subjects showed grea ST segment depression during digoxin al compared to combination therapy The third subject had only a modest amount of ST segm depression (1 mm) during both digoxin a combination therapy Mean exercise heart ra results in this group were similar to the nor subjects and other CAD patients Thus maxi mum exercise heart rate during propranol (110 ± 5.7 beats/min) or combination therap (108 ± 6.7 beats/min) was significantly reduced compared to the control value of 142 ± 7.6 be min ($p < .001$ for both comparisons) wh maximum exercise heart rate during digox therapy was 138 ± 8.1 beats/min, not signi cantly different than the control value

Of all 16 subjects (eight controls eight CAD with a non ischemic control exercise ST segme response to exercise a total of seven developed i ischemic response during combination therapy during digoxin treatment alone Thus the in dence of a "false positive" exercise test induce by digoxin was 44 per cent This of course pres poses that the positive test in the CAD patien does not represent true ischemia In the se subjects with "false positive" tests the maximu amount of exercise ST segment depression w greater during digoxin than during combina therapy in six and unchanged in one

Discussion

Acute intravenous administration of either propranolol or digoxin has been shown to result in significantly different effects than prolonged oral therapy[4,5] We have previously proposed that in the case of oral propranolol therapy this may relate to circulatory adjustments which do not occur when the drug is given acutely[4] Since the majority of patients receiving these drugs undergo chronic oral therapy analysis of the effect of propranolol and digoxin that are most relevant to the usual clinical situation require assessment

sion Digoxin or P/D both uniformly increased the maximum amount of ST segment depression which was greater with digoxin than P/D However the maximum heart rate on P/D was significantly reduced as compared to that on digoxin It is concluded that (1) CAD patients are more sensitive to propranolol or digoxin induced AV block than normals (2) propranolol does not change the magnitude of ischemic exercise ST segment depression (3) digoxin increases ischemic exercise ST segment depression and results in a high incidence of false positive exercise tests and (4) the addition of propranolol to digoxin attenuates the effects of digoxin on the exercise ST segment

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REFERENCES

1. Stern S and Eisenberg S The effect of propranolol (Inderal) on the electrocardiogram of normal subjects Am Heart J 77 192 1969
2. Dwyer E M Jr Weiner L and Cox J W Effects of beta adrenergic blockade (Propranolol) on left ventricular hemodynamics and the electrocardiogram during exercise induced angina pectoris Circulation 28 50 1968
3. Prichard B N C and Gillam P M S Assessment of propranolol in angina pectoris Clinical dose response curve and effect on electrocardiogram at rest and in exercise Br Heart J 33 473 1971
4. LeWinter M M Crawford M H Karliner J S and O'Rourke R A Effects of oral propranolol in normal subjects Clin Pharmacol Ther 17 709 1975
5. Lipman B S Massie E and Kleiger R E Clinical scalar electrocardiography Chicago 1972 Year Book Medical Publishers Inc p 270
6. Nordstrom Ohrberg G Effect of digitalis glycosides on electrocardiogram and exercise test in healthy subjects Acta Med Scand 176(Suppl 420) 1 1964
7. Crawford M H LeWinter M M O Rourke R A, Karliner J S and Ross J R Jr Combined propranolol and digoxin therapy in angina pectoris Ann Intern Med 83 449 1975
8. Doan H E Peterson D R Blackman J R and Bruce R A Myocardial ischemia after maximal exercise in healthy men Am Heart J 69 11 1965
9. Smith T W Butler V P Jr, and Haber E Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay N Engl J Med 281 1212 1969
10. Shand D G Nuckolls E M, and Oates J A Plasma propranolol levels in adults with observations in four children Clin Pharmacol Ther 11 112, 1970
11. Lewis A Biostatistics New York 1966 Reinhold Publishing Corporation p 52
12. Williams, M H Jr Zohman L R, and Ratner A C Hemodynamic effects of cardiac glycosides in normal human subjects during rest and exercise J Appl Physiol 13 417 1958
13. Eckberg D L Drabinsky M, and Braunwald E Defective cardiac parasympathetic control in patients with heart disease N Engl J Med 285 877 1971
14. MacAlpin R N Kattus A A, and Winfield M E The effect of a β adrenergic blocking agent (Nethalide) and nitroglycerin on exercise tolerance in angina pectoris Circulation 31 869 1965
15. Russek H I Propranolol and isosorbide dinitrate synergism in angina pectoris Am J Cardiol 21 44 1968
16. Mahler F Karliner J S and O'Rourke R A Effects of chronic digoxin administration on left ventricular performance in the normal conscious dog Circulation 50 720 1974
17. Nasrallah A Garcia E Benrey J and Hall R J Treadmill exercise testing in the presence of nonspecific ST T changes or digitalis effect Correlation with coronary angiography Am J Cardiol (Abstr) 35 160 1975

ischemia might be masked by beta blockade is not supported by our results.

In patients with ischemic control exercise tests, digoxin, alone or in combination with propranolol, resulted in a significant and virtually uniform increase in the amount of ST segment depression. It is not clear whether this phenomenon is similar to that reported in individuals with digitalis induced 'false positive' exercise tests,[6] or in fact represents worsening ischemia during exercise. The latter hypothesis would be consistent with the drug's effect of increasing contractility and thereby myocardial oxygen demands in the nonfailing left ventricle.[10] Since the incidence of digitalis induced "false positive" tests in our series of normal subjects was only 50 per cent, it might be argued that the rather uniform nature of the ST segment response to digitalis in CAD subjects with ischemic exercise responses indicates that increased ischemia was at least partially responsible for the ST segment depression. This question is only answerable by using some other marker for the extent of ischemia.

The CAD patients with non-ischemic control exercise tests whose tests became positive while receiving digoxin constitute a separate group. The question as to whether this represents a "false positive" response or induction of increased ischemia by digoxin is once again difficult to answer. The fact that the response was not a uniform one, as it was in the patients with positive control tests, and that the incidence (three of eight patients) was similar compared with the normal group, suggests but does not prove that the phenomenon represents a "false positive" response. As indicated earlier, some other marker for ischemia is necessary to resolve the question.

The incidence of ischemic ST segment exercise responses in our eight normal individuals with non-ischemic control exercise tests during digoxin therapy was 50 per cent. The maximum amount of exercise ST segment depression did not correlate with the serum digoxin concentrations in this group. Although the sample size is small, these results suggest that "false positive" digitalis induced exercise tests are to be expected in many patients receiving digitalis and that this phenomenon may represent an idiosyncratic rather than a serum level-related phenomenon. Since no normal subject with a "false positive" exercise response during digoxin treatment had more than 2.5 mm. of maximum ST segment depression when resting ST segment changes were taken into account, it is possible that there may be a separation between 'false' and 'true' positives at some absolute level of ST segment depression. This suggestion has been made by other investigators and is supported by our data, though the small sample size precludes definite conclusions.

Finally, our results suggest that the magnitude of the effects of digoxin on the exercise ST segment are in part rate related, since in most cases combination therapy resulted in less ST segment depression than digoxin alone. Since propranolol did not appear specifically to affect the ST segment other than to delay the appearance of depression, it may be that the reduced rate produced by beta adrenergic blockade was responsible for the less striking nature of the changes during combination therapy. If this is the case, the incidence of digoxin induced false positive ischemic responses to exercise may also be a function of the extent to which the patient is stressed and approaches his maximal heart rate.

Summary

The effects of propranolol, digoxin, and combination therapy (P/D) on the resting and exercise ECG were studied in ten normal subjects and patients with coronary artery disease (CAD) given a sequence of oral placebo, propranolol, P/D, digoxin, and placebo for two week periods. Digoxin produced a significant decrease in T wave amplitude and often resulted in ST segment depression in the resting ECG. Propranolol, digoxin, and P/D tended to decrease the QTc interval and prolong the PR interval. However, CAD patients were more sensitive to PR prolongation than normals while receiving propranolol or digoxin alone. Propranolol therapy did not significantly affect the ST segment of the exercise ECG in the normal subjects or the CAD patients without an ischemic control exercise ECG. By contrast, 50 per cent of the normal subjects developed "false positive" ischemic ST segment responses to exercise while receiving digoxin or P/D and three of eight CAD patients without ischemic control exercise ST segments had a similar response to digoxin or P/D. In the CAD patients with ischemic control exercise ST segments, propranolol did not affect the amount of ST segment depression at the onset of angina or the maximum amount of ST segment depre-

...sion Digoxin or P/D both uniformly increased the maximum amount of ST segment depression which was greater with digoxin than P/D. However the maximum heart rate on P/D was significantly reduced as compared to that on digoxin. It is concluded that (1) CAD patients are more sensitive to propranolol or digoxin induced AV block than normals (2) propranolol does not change the magnitude of ischemic exercise ST segment depression (3) digoxin increases ischemic exercise ST segment depression and results in a high incidence of false positive exercise tests and (4) the addition of propranolol to digoxin attenuates the effects of digoxin on the exercise ST segment.

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REFERENCES

1. Stern S. and Eisenberg S. The effect of propranolol (Inderal) on the electrocardiogram of normal subjects. Am. Heart J. 77 19? 196?
2. Dwyer E. M. Jr., Weiner L. and Cox J. W. Effects of beta adrenergic blockade (Propranolol) on left ventricular hemodynamics and the electrocardiogram during exercise induced angina pectoris. Circulation 28 250 1968
3. Prichard B. N. C. and Gillam P. M. S. Assessment of propranolol in angina pectoris. Clinical dose response curve and effect on electrocardiogram at rest and in exercise. Br Heart J 33 4 3 1971
4. LeWinter M. M. Crawford M. H. Karliner J. S. and O'Rourke R. A. Effects of oral propranolol in normal subjects. Clin Pharmacol Ther 17 09 19 5
5. Lipman B. S., Massie E., and Kleiger R. F. Clinical scalar electrocardiography Chicago 1972 Year Book Medical Publishers Inc. p. 270
6. Nordstrom-Ohrberg G. Effect of digitalis glycosides on electrocardiogram and exercise test in healthy subjects. Acta Med Scand 176(Suppl 420) 1 1964
7. Crawford M. H., LeWinter M. M. O'Rourke R. A., Karliner J. S. and Ross J. R. Jr. Combined propranolol and digoxin therapy in angina pectoris. Ann Intern Med 83 449 19 5
8. Doan H. E. Peterson D. R. Blackman J. R. and Bruce R. A. Myocardial ischemia after maximal exercise in healthy men. Am. Heart J. 69 11 1965
9. Smith T. W., Butler V. P., Jr., and Haber E. Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. N. Engl. J. Med. 281 1212, 1969
10. Shand D. G. Nuckolls E. M. and Oates J. A. Plasma propranolol levels in adults with observations in four children. Clin Pharmacol Ther 11 112 1970
11. Lewis A. Biostatistics, New York 1966 Reinhold Publishing Corporation p. 52
12. Williams M. H. Jr., Zohman L. R. and Ratner A. C. Hemodynamic effects of cardiac glycosides in normal human subjects during rest and exercise. J. Appl. Physiol 13 417 1958
13. Eckberg D. L. Drabinsky M. and Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. N. Engl. J. Med. 285 877 1971
14. MacAlpin R. N., Kattus A. A. and Winfield M. E. The effect of a β adrenergic blocking agent (Nethalide) and nitroglycerin on exercise tolerance in angina pectoris. Circulation 31 869 1965
15. Russek H. I. Propranolol and isosorbide dinitrate synergism in angina pectoris. Am. J. Cardiol. 21 44 1968
16. Mahler F. Karliner J. S. and O'Rourke R. A. Effects of chronic digoxin administration on left ventricular performance in the normal conscious dog. Circulation 50 ? 0 19 4
17. Nasrallah A. Garcia F. Benrey J. and Hall R. J. Treadmill exercise testing in the presence of nonspecific ST-T changes or digitalis effect. Correlation with coronary angiography. Am. J. Cardiol. (Abstr.) 35 160 19 5

Table I Coronary flows

	Right ventricle		Septum	Left ventricle	
	TTI	Flow	Flow	Flow	TTI
Group I (n = 8)					
Control	684 ± 198	65 ± 11	106 ± 23	110 ± 24	2900 ± 416
Septal ligation	646 ± 198	51 ± 15	57 ± 13	89 ± 16	2766 ± 450
Group II (n = 8)					
Control	64[illegible] ± 90	74 ± 16	115 ± 20	112 ± 18	2964 ± 10[illegible]
RCA ligation	[illegible]0 ± 210	44 ± 8	102 ± [illegible]	105 ± 2[illegible]	3093 ± 1090

Values are m a s _ one standard d v t n Te on tim indices (TTI) a e in units of mm Hg sec min coronary fl w in units of ml/min 100 Gm An asterisk ind ates $p < 0.0$ d ff rence from cont ol

output was recorded from 13 to 16 mm internal diameter electromagnetic flow transducers (Statham model SP 2202) placed around the ascending aorta The flow transducers were calibrated in vitro with timed volume collections of blood

In the septal coronary ligation studies the left main coronary artery and the proximal portions of the left anterior descending and circumflex coronary arteries were dissected free A 4 0 silk ligature was placed around the main septal branch in such a manner as not to constrict the other major coronary arteries In the right coronary ligation studies a 4 0 silk ligature was placed around the right main coronary artery within 2 0 cm of its origin The pericardial incisions were partly sutured closed to contain the right ventricle within the pericardial space during acute fluid infusions

Regional myocardial blood flow was measured by injecting differently labeled batches of radioactive microspheres (400 000 to 600 000 per injection) into the left atrium as described previously Microspheres with a mean diameter of 9μ labeled with Ce Sr Sc as well as 15μ diameter microspheres labeled with I were used to measure regional myocardial blood flow The suspension fluid was counted before using each batch of microspheres to be certain that no free isotope was present A small Holter pump was used to withdraw reference samples (timed volume collections) from the femoral arteries during the microsphere injections Since well mixed microspheres are distributed to regions in proportion to flow regional myocardial flow was determined from the equation myocardial flow equals myocardial nuclide activity × reference sample flow/reference sample nuclide activity

Because coronary flow is influenced by changes in oxygen content hemoglobin concentration was determined with each flow measurement At the end of each experiment the dog was killed and the heart removed The coronary arteries were opened from the ostia distally and examined for completeness of occlusion Only dogs with complete occlusion of the appropriate coronary vessels without constriction of adjacent coronary arteries were included The atria valves great arteries large coronary vessels and epicardial fat were removed from the ventricles The free wall of the right ventricle was cut at its junction with the ventricular septum The free wall of the left ventricle and the septum were separated at the right border of the posterior papillary muscle posteriorly and along the left anterior descending coronary artery anteriorly The papillary muscles were included as part of the left ventricular free wall The tissue from each region was placed in one or more vials weighed and counted in a well scintillation counter The radioactivity emitted from each nuclide was determined by the method of Rudolph and Heymann modified by using different calibration constants for differential spectrometry

Measurements were made during the control state in each dog during septal coronary arterial ligation in eight dogs (Group I) during right coronary arterial ligation in eight dogs (Group II) None of the animals required resuscitation after coronary ligation During the control and ischemic periods the pressure in the right atrium was elevated to fixed levels by rapid infusion of fresh warmed blood Right atrial pressure was maintained at three specific levels for 30 seconds before measurements of intravascular pressure and cardiac output were recorded At the completion of each function curve 50 to 150 ml of whole blood were removed until cardiac output equalled

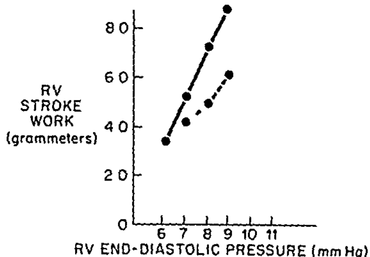


Fig. 1. Changes in right ventricular (RV) function curves during septal coronary ligation. These curves were derived by averaging the stroke work values at pressure levels common to all curves in a group. Solid line represents control values; dashed line, ligation values. Note significant change ($p < 0.05$) in the right ventricular curve occurred with septal ligation.

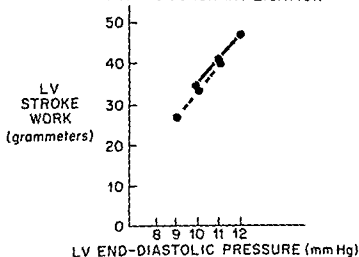


Fig. 2. Changes in left ventricular (LV) function curves during septal coronary ligation. Solid line represents control values; dashed line, ligation values. Note the left ventricular curve did not change with septal ligation.

that during the mid control level. Regional myocardial blood flow determinations were made at these points during control and coronary arterial ligation periods (14 to 16 minutes after ligation). Changes in myocardial oxygen demand were estimated from the ventricular tension time indices (TTI), measured by planimetry of the area beneath the systolic portion of the aortic and right ventricular pressure tracings.[1,4] For the left

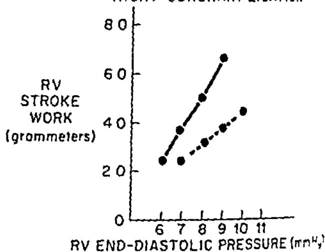


Fig. 3. Changes in right ventricular function curves during right coronary ligation. Solid line represents control values; dashed line, ligation values. Note significant ($p < 0.05$) shift in right ventricular curve occurred with right coronary ligation.

ventricle this area began with aortic systole and ended with the aortic dicrotic notch; for the right ventricle the area began with onset of isovolumetric contraction and ended on the diastolic down slope at the same pressure level. All tension time indices were expressed as mm Hg second per minute. Ventricular stroke work in grammeters was calculated after each increase in atrial pressure by the formula: stroke work = stroke volume (ml.) × mean ventricular systolic − mean diastolic pressure. Ventricular function curves were plotted by correlating right and left ventricular end diastolic pressures with ventricular stroke work. Average function curves were derived by averaging the stroke work values at pressure levels common to all curves. The mean postligation curves were compared with the corresponding mean control curves. Statistical comparisons in this study were made by paired t tests; changes in the ventricular function curves were compared by analysis of covariance of the slopes and intercepts of the curves.[13]

Results

Group I. Total occlusion of the septal coronary artery resulted in a 46 per cent decrease in flow to the ventricular septum (Table I). Following septal coronary ligation, the average right ventricular function curve shifted significantly ($p < 0.05$) to the right, indicating impairment of right ventricular performance (Fig. 1). The

Table II Hemodynamic findings during coronary flow determinations*

	Heart rate (beats/min)	Stroke volume (ml)	Pressures (mm Hg) Right atrial	R ventricle systolic	R ventricl end-diastolic	Left atrial	Aortic Systolic	Aortic Diastolic
Group I								
Control	146 ± 19	17 ± 3	5 ± [illegible]	28 ± 8	8 ± 6	10 ± 3	130 ± 10	87 ± [illegible]
Septal ligation	129 ± 29	12 ± 4	6 ± [illegible]	25 ± 7	[illegible] ± 2	10 ± 3	12[illegible] ± 15	83 ± 10
Group II								
Control	125 ± 26	18 ± 7	6 ± 2	28 ± 5	7 ± 2	11 ± 2	147 ± 24	90 ± 26
RCA ligation	11[illegible] ± 38	16 ± 7	7 ± 3	25 ± 5	9 ± 3	9 ± 3	132 ± 14	100 ± [illegible]

Values are means ± one standard deviation Asterisk indicates $p < 0.05$ difference from control value

average left ventricular function curve did not change significantly (Fig 2) Coronary flow to the right and left ventricular free walls fell 21 and 19 per cent respectively probably secondary to the decrease in heart rate and ventricular tension time indices During septal ischemia no significant changes were seen in right atrial left atrial or aortic pressures or in stroke volumes (Table II) Hemoglobin concentrations averaged 12 7 ± 2 4 (S D) Gm per 100 ml for controls and 13 1 ± 2 6 Gm per 100 ml with septal ligation Arterial P_{O_2} exceeded 150 mm Hg in all animals therefore the changes in coronary flows were not secondary to changes in arterial oxygen content

Group II Total occlusion of the proximal right coronary artery resulted in 41 per cent decrease in flow to the free wall of the right ventricle (Table I) Following right coronary arterial ligation the average right ventricular function curve shifted significantly ($p < 0.05$) to the right indicating impairment of right ventricular performance (Fig 3) Coronary flow to the left ventricular free wall and to the ventricular septum did not change significantly (Table I) During right ventricular ischemia no significant changes were seen in stroke volume right atrial left atrial or aortic pressures however right ventricular end diastolic pressure did increase significantly (Table II) Hemoglobin concentrations did not significantly change averaging 12 4 ± 3 3 Gm per 100 ml for controls and 11 2 ± 3 4 Gm per 100 ml with right coronary arterial ligation

Discussion

To our knowledge this is the first report demonstrating a significant impairment of right ventricular function following isolated septal ischemia Early studies by other investigators failed to demonstrate significant depression of ventricular function following injury to the right ventricular free wall[3] Recently Brooks and associates were unable to show changes in ventricular pressure or aortic flow following total occlusion of the right coronary artery but using an isometric strain gauge arch they did demonstrate a decrease in right ventricular contractile force

The present study shows that right ventricular function was impaired as much with septal ligation as with right coronary arterial ligation (Figs 1 and 3) Right ventricular volumes were not measured therefore the function curves presented here plot stroke work against end diastolic pressure rather than end diastolic volume Myocardial ischemia may produce significant abnormalities in the diastolic properties of ventricular muscle Forrester and associates[1] have shown that although left ventricular wall stiffness may increase late in the course of myocardial infarction they found it was significantly decreased acutely 1 hour after infarction As a result of this early decrease in stiffness left ventricular end diastolic pressure may be lower for any given end diastolic volume Therefore the rightward shifts in the right ventricular function curves shown in Figs 1 and 3 may underestimate the degree of impairment which occurred following right and septal coronary ligation

The mechanism responsible for maintaining right ventricular output and pressure following severe injury to the right ventricular free wall has not been well defined Bakos[4] suggested that the architecture of the ventricular muscle may explain the supportive role of the septal contrac

tion in right ventricular function Robb and Robb[11] pointed out that the deep sinospiral *muscle band forms the main mass of the right* ventricular free wall and also enters into the formation of the ventricular septum This encir cling arrangement around the ventricular cham ber may allow the tension developed by contrac tion of an undamaged portion to be transmitted to the chamber thereby generating right ventric ular systolic pressure In this study the free wall of the *right ventricle weighed an average of 35 9* Gm and the ventricular septum 35 8 Gm Liga tion of the right or septal coronary artery reduced coronary flow by 41 and 46 per cent to the right ventricular free wall and septum, respectively If each region contributes an equal amount to right ventricular ejection then equivalent degrees of ischemic injury may produce nearly equivalent degrees of right ventricular dysfunction Since similar degrees of right ventricular impairment did occur, the data from this study tend to suggest that normal septal contraction contrib utes to right ventricular function nearly as much as does contraction of the free wall

Ligation of the septal coronary artery did not significantly change the left ventricular function curves shown in Fig 2 This may be explained by the fact that only a small portion of the total left ventricular mass was made ischemic by ligation of the septal coronary artery The mass of the ventricular septum was approximately half that of the left ventricular free wall and thus repre sented one third of the total left ventricular contractile unit (left ventricular free wall and septum) Since coronary flow to the septum itself *was decreased* by 46 per cent the extent of ischemia to the total left ventricular contractile unit was relatively small

Coronary flow to the left ventricular free wall fell by 20 per cent following ligation of the septal coronary artery The small decrease in left ventricular myocardial flow however did not alter the left ventricular function curve as is shown in Fig 2 The coronary flow changes were probably secondary to the decreases in heart rate and tension time index for Sarnoff and co work ers[1] have demonstrated a linear relationship between these factors and coronary blood flow Coronary flow to the right ventricular free wall likewise fell by 22 per cent following septal coronary arterial ligation This also was asso ciated with similar decreases in heart rate and right ventricular tension index as occurred in the *left ventricle*

Summary

This study indicates that in dogs ischemic injury to just the ventricular septum has little effect on left ventricular function The data demonstrate that ischemic injury to either the right ventricular free wall or the ventricular *septum alters right ventricular* function and compliance, suggesting that both regions play a role in maintaining right ventricular perform ance That septal contraction supports right ventricular function may explain why in early studies right ventricular pressure development and output were little affected by severe injury to the free wall

The authors wish to express their appreciation to Frank T Jones and Douglas Huffines for their excellent technical assistance

REFERENCES

1 Fixler D F Archie J P Jr Ullyot D J Buckberg C D and Hoffman J I F Effects of acute right ventricular systolic hypertension on regional myocardial blood flow in anesthetized dogs AM HEART J 85 [illegible] 1973

2 Starr I Jeffers W A and Mead R H The absence of conspicuous increments in venous pressure after severe damage to the right ventricle of the dog with a discussion of the relation between clinical congestive failure and heart disease AM HEART J 26 291 1943

3 Kagan A Dynamic responses of the right ventricle following extensive damage by cauterization Circulation 5 816 1952

4 Bakos A C P The question of the function of the right ventricular myocardium An experimental study Circulation 1 724 1950

5 Brooks H Kirk F S Vokonas P S Urschel C W and Sonnenblick F H Performance of the right ventricle under stress relation to right coronary flow J Clin Invest 50 2176 1971

6 Fixler D F Archie J P Jr Ullyot D J and Hoffman J I F Regional coronary flow with increased right ventricular output in anesthetized dogs AM HEART J 86 788 1973

7 Monroe G A Knapp R S Fixler D E and Mullins C B Effect of acute pulmonary arterial obstruction on right ventricular volume and coronary flow in closed chest anesthetized dogs Circulation 48(Suppl IV) 1[illegible] 1973

8 Blair E Anatomy of the ventricular coronary arteries in the dog Circulation 9 333 1961

9 Domenech R J Hoffman J I F Noble M I M Saunders K B Henson J R and Subijanto S Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs Circ Res 25 581 1969

10 Buckberg G D Luck J C Payne D B Hoffman

J I F Archie J P Jr and Fixler D E Some sources of error in measuring regional blood flow with radioactive microspheres, J Appl Physiol 31 598 1971
11 Rudolph A M and Heymann M A Circulation of the fetus in utero methods for studying distribution of blood flow cardiac output and organ blood flow Circ. Res 21 163 1967
12 Sarnoff S J Braunwald F Welch G H Jr Case R B Stainsby W N and Macruz, R Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension time index Am J Physiol 192 148 1958
13 Snedecor G W., and Cochran W G Statistical methods Ames 1967 The Iowa State University Press pp 419 466
14 Forrester J S Diamond G Parmley W W., and Swan H J C Early increase in left ventricular compliance after myocardial infarction J Clin Invest 51 598 1972
15 Robb J S and Robb R C The normal heart—Anatomy and physiology of the structural units AM HEART J 23 455 1942

A depressed response of left ventricular contractile force to isoproterenol and norepinephrine in dogs with congestive heart failure

Walter H. Newman, Ph.D.
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Numerous studies have demonstrated that the norepinephrine content of cardiac tissue from man and animals with congestive heart failure is markedly reduced.[1-3] This reduction in norepinephrine stores has been shown to be associated with a depressed inotropic response to tyramine in papillary muscles taken from patients with heart failure.[4] Additionally, the inotropic effect of cardioaccelerator nerve stimulation was found to be reduced in dogs with heart failure.[5] In these same dogs, the inotropic response to one dose of exogenously administered norepinephrine was found to be normal. Since in these previous studies no dose response to exogenous norepinephrine was determined in intact animals and since the sympathetic nervous system is thought to play a role in maintaining homeostasis in heart failure, the present investigations were undertaken to examine the dose response relationships of two β agonists in dogs with congestive heart failure.

Methods

In each of five mongrel dogs (21 to 34 kilograms) a 1.5 cm. infrarenal aortocaval fistula was created. At the time of experimentation (7 to 22 weeks after surgery) two dogs had ascites and limb edema and all had significantly elevated pulmonary wedge pressures (PWP). Five normal dogs (17 to 27 kilograms) served as controls.

The dogs were anesthetized with Na pentobarbital (30 mg. per kilogram); respiration was maintained with 100 per cent O_2, a cuffed endotracheal tube, and a Harvard respirator. Arterial pH was maintained between 7.35 and 7.45 by altering respiratory rate. Prior to thoracotomy, PWP was measured with a Swan-Ganz catheter passed through the right jugular vein and connected to a Statham P23db pressure transducer. Following this measurement, the catheter was withdrawn to a point just outside the right atrium and used for drug administration. Carotid artery pressure was measured with a Statham P23db transducer connected to a catheter in the left carotid artery. Bilateral vagotomy was performed in the neck. Heart rate was recorded with a tachometer of our own design.

A left thoracotomy was performed and the pericardium was opened and sutured to the chest wall. A modified Walton-Brodie strain gauge arch was attached to the left ventricle. The modification to the arch consists of altering the manner of attachment of the arch. Instead of sutures, three steel pins 2 cm. long were placed in each foot of the arch. The pins were arranged in two rows perpendicular to the long axis of the arch. When placed on the ventricle, the pins penetrated the ventricular wall. This manner of attachment has been previously reported.[6] The arch was attached to the ventricular free wall in an area free of papillary muscles and oriented in a direction approximately perpendicular to the anterior descending coronary artery. The muscle segment subtended by the arch was stretched to the peak of the length-tension curve and fixed at this length. Changes in contractile force were expressed as per cent above control.

Levophed (norepinephrine bitartrate, Winthrop Laboratories, New York, N. Y.) was administered by rapid intravenous bolus injection in the

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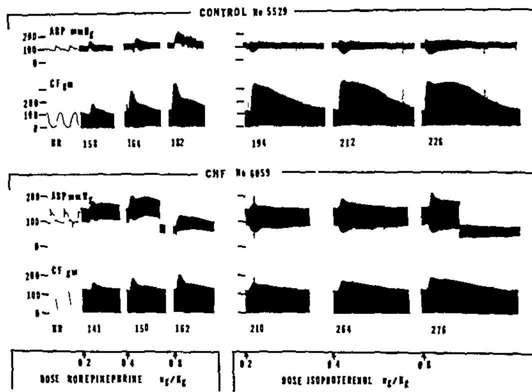


Fig 1 Typical response of carotid artery blood pressure (ABP) left ventricular contractile force (CF) and heart rate (HR) to norepinephrine and isoproterenol in a control dog and a dog with congestive heart failure (CHF) ABP attenuated from ×10 to ×20

Table I Ventricular measurements from normal and CHF dogs

	BW (Kg)	LVW (Gm.)	LVh (cm)	LVd (cm)	RVW (Gm)	RVh (cm)
Control	22.3	101.3	1.32	3.5	32.0	0.55
(N = 5)	±1.6	±4.3	±0.04	±0.19	±1.6	±0.05
CHF	27.0	130.9	1.68	4.5	43.2	0.6
(N = 5)	±2.4	±4.6	±0.14	±0.19	±26	±0.04
P	NS	<0.005	<0.05	<0.01	<0.01	<0.01

Measurements taken from the left and right ventricles of control and CHF dogs. BW Body weight LVW Left ventricular weight LVh LV free wall thickness LVd, LV inter... shortest axis diameter at midplane RVW right ventricular weight RVh RV wall thickness Values are mean ± S.E.

following sequence and doses of the base 0.0125 0.025 0.05 0.10 0.20 0.40 0.80 and 1.6 µg per kilogram Isoproterenol HCl (Isuprel Winthrop Laboratories New York N Y) was administered in the same manner and dosage schedule Following the administration of each dose of either drug all parameters were allowed to return to control levels before the next dose was administered The order of administration of the dosage

Table II Response to norepinephrine

Dose NE (µg/Kg)	ΔCF (%)	ADBP (mm Hg)	ΔADBP (mm Hg)	HR (beats/min)
Control (N = 5) dogs				
0.0125	5.6 ± 2.2	108 ± 4.9	10 ± 0	167 ± 7.8
0.025	7 ± 2.3	116 ± 6.0	12 ± 2.0	165 ± 6.6
0.05	18.0 ± 4.8	118 ± 7.3	18 ± 2.5	164 ± 6.7
0.10	40.0 ± 8.1	125 ± 6.8	21 ± 1.9	166 ± 3.8
0.20	83.1 ± 8.8	132 ± 5.1	28 ± 1.2	168 ± 3.5
0.40	125.0 ± 11.1	145 ± 6.1	41 ± 2.9	176 ± 4.2
0.80	168.6 ± 14.7	167 ± 9.7	58 ± 5.8	201 ± 10.0
1.60	199.0 ± 20.8	180 ± 7.7	6 ± 6.8	216 ± 5.9
CHF (N = 5) dogs				
0.0125	0	67 ± 10.2	5 ± 0	15 ± 10.5
0.025	3.8†	69 ± 11.1	7 ± 1.6	1 ± 10.3
0.05	4.4 ± 3.9†	71 ± 10.2	8 ± 1.7	154 ± 9.4
0.10	11.3 ± 2.4‡	78 ± 11.0	14 ± 3.2	154 ± 9.2
0.20	60 ± 6.6‡	84 ± 12.1	21 ± 4.3	156 ± 8.9
0.40	46.0 ± 9.9‡	91 ± 18.3	29 ± 9.6	166 ± 10.5
0.80	71.0 ± 21.1‡	114 ± 20.6	50 ± 14.1	179 ± 10.1
1.60	73.0 ± 20 ‡	121 ± 21.2	5 ± 13.4	202 ± 9.5

Values are mean ± S.E. %ΔCF Per cent change above control level ADBP arterial diastolic blood pressure (carotid artery) HR heart rate

$P < 0.05$
†$P < 0.0$
‡$P < 0.00$ compared to control response

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In each of five mongrel dogs (21 to 34 kilograms) a 1 5 cm infrarenal aortocaval fistula was created At the time of experimentation (7 to 22 weeks after surgery) two dogs had ascites and limb edema and all had significantly elevated pulmonary wedge pressures (PWP) Five normal dogs (17 to 27 kilograms) served as controls

The dogs were anesthetized with Na pentobarbital (30 mg per kilogram) respiration was maintained with 100 per cent O a cuffed endotracheal tube, and a Harvard respirator Arterial pH was maintained between 7 35 and 7 45 by altering respiratory rate Prior to thoracotomy PWP was measured with a Swan Ganz catheter passed through the right jugular vein and connected to a Statham P23db pressure transducer Following this measurement the catheter was withdrawn to a point just outside the right atrium and used for drug administration Carotid artery pressure was measured with a Statham P23db transducer connected to a catheter in the left carotid artery Bilateral vagotomy was performed in the neck Heart rate was recorded with a tachometer of our own design

A left thoracotomy was performed and the pericardium was opened and sutured to the chest wall A modified Walton Brodie strain gauge arch was attached to the left ventricle The modification to the arch consists of altering the manner of attachment of the arch Instead of sutures three steel pins 2 cm long were placed in each foot of the arch The pins were arranged in two rows perpendicular to the long axis of the arch When placed on the ventricle the pins penetrated the ventricular wall This manner of attachment has been previously reported [6] The arch was attached to the ventricular free wall in an area free of papillary muscles and oriented in a direction approximately perpendicular to the anterior descending coronary artery The muscle segment subtended by the arch was stretched to the peak of the length tension curve and fixed at that length Changes in contractile force were expressed as per cent above control

Levophed (norepinephrine bitartrate Winthrop Laboratories New York N Y) was administered by rapid intravenous bolus injection in the

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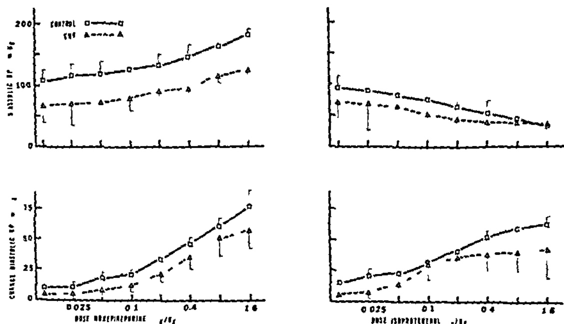


Fig 3 Dose response curves showing the effect of congestive heart failure (CHF) on the response of carotid artery diastolic blood pressure to norepinephrine and isoproterenol P < 0 05

force in both control and CHF dogs These data indicate a significantly reduced response of contractile force to both norepinephrine and isoproterenol at all dose levels in dogs with CHF For example at the norepinephrine dose level of 0 8 μg per kilogram the mean response of contractile force in the control dogs was 168 6 ± 14 7 per cent above control with a range of 166 to 200 per cent In the CHF animals the same dose of norepinephrine produced a mean increase in contractile force of 71 0 ± 21 3 per cent with a range of 25 to 130 per cent At the same dose level of isoproterenol the mean response of contractile force was 251 ± 14 4 per cent with a range of 201 to 283 per cent in control dogs This same dose of isoproterenol 0 8 μg per kilogram produced a mean increase in contractile force of 92 ± 31 5 per cent with a range of 21 to 201 per cent in dogs with CHF An overlap in the individual dose response curves from control and CHF dogs occurred in only one animal with CHF This dog had no ascites or limb edema and the lowest PWP 16 mm Hg of the CHF group

Response of heart rate to norepinephrine and isoproterenol In the five control dogs heart rate (HR) prior to the administration of drugs was 168 ± 17 5 beats per minute In the CHF group HR was 151 ± 10 5 beats per minute These two values were not significantly different The effects of all doses of norepinephrine and isoproterenol

Table III Response to isoproterenol

Dose ISO (μg/Kg)	ΔCF (%)	ADBP (mm. Hg)	ΔADBP (mm Hg)	HR (beats/min)
Control (N = 5) dogs				
0 0125	27 ± 4 7	96 ± 10 0	15	165 ± 7 5
0 025	60 ± 8 9	90 ± 10 4	19 ± 3 2	1[illegible] ± 8 [illegible]
0 0[illegible]	86 ± 9 9	8[illegible] ± 11.2	23 ± [illegible]8	178 ± 8 7
0 10	135 ± 14 6	[illegible] ± 10 1	30 ± 4 [illegible]	185 ± 9 3
0 20	18[illegible] ± 11 7	64 ± 9 5	41 ± 4 3	20[illegible] ± 7 1
0 40	[illegible]29 ± 11.2	53 ± 9 0	[illegible] ± 4 1	2[illegible]6 ± 9 6
0 80	[illegible]51 ± [illegible]4 6	46 ± 7 3	59 ± 4 0	237 ± 10 1
1 60	244 ± [illegible]4 5	33 3 ± 1 6	63 ± 7 [illegible]6	261 ± 10 9
CHF (N = 5) dogs				
0 0125	7 ± 3 †	0 ± 17 9	5	162 ± 9 9
0 025	16 ± 6 6‡	68 ± 18 0	7 ± 1 6	169 ± 11 1
0 05	29 ± 8 8‡	63 ± 20 1	13 ± 1 7	174 ± 12.4
0 10	40 ± 13 9‡	[illegible]0 ± 11.3	30 ± 12 5	189 ± 9 7
0 20	59 ± 18 5‡	44 ± 4 9	35 ± 16 7	209 ± 10 9
0 40	81 ± 28 3‡	40 ± 3 [illegible]	36 ± 15 1	23[illegible] ± 15 3
0 80	9[illegible] ± 31 5‡	41 ± 4 3	37 ± 14 7	153 ± 15 2
1 60	113 ± [illegible]5 3‡	35 ± 3 5	41 ± 23 3	259 ± 14 [illegible]

Abbreviations same as in Table II

on heart rate are shown in Tables II and III The dose response curves for heart rate are shown in Fig 2 There was no significant difference in the response of heart rate to any dose of norepinephrine or isoproterenol between the control and CHF groups For instance at the 0 8 μg per kilogram dose level norepinephrine produced a mean heart rate of 201 ± 10 beats per minute

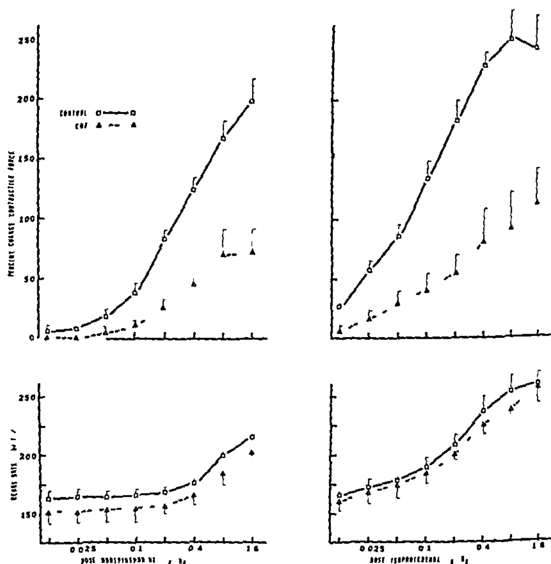


Fig 2 Dose response curves showing the effect of congestive heart failure (CHF) on the response of left ventricular contractile force and heart rate to norepinephrine and isoproterenol $P < 0.05$

regimens of the two agents was alternated with each dog

Following the completion of the experiment the heart was arrested with pentobarbital and removed The atria were cut away The right ventricle was separated from the left ventricle and both were weighed and measured The left ventricle was divided along a plane midway and perpendicular to the long axis Left ventricular diameter was measured as a short axis diameter from endocardium to endocardium of the cut left ventricle Left ventricular wall thickness was measured from the cut surface on two sites of the free wall Right ventricular wall thickness was measured on the cut surface of the right ventricular free wall

All data were statistically analyzed with Student s t test for unpaired data

Results

Ventricular measurements Table I shows the results from measurement of the left and right ventricle The response to chronic volume over load produced by the fistula was characterized by a significant increase in left ventricular mass diameter and wall thickness indicating cardiac hypertrophy Pulmonary wedge pressures averaged 4 5 mm Hg (range 2 to 6 mm Hg) in the control dogs and 19 6 mm Hg (range 16 to 23 mm Hg) in dogs with CHF

Response of contractile force to norepinephrine and isoproterenol In the five control dogs contractile force prior to drug treatment was 92 ± 9 1 Gm and in the CHF dogs was 118 ± 16 Gm The values were not significantly different and were assigned 100 per cent Fig 1 is a typical recording from a control dog and a dog with CHF and shows the response of the measured parameters to the administration of isoproterenol and norepinephrine at dose levels of 0 2 0 4, 0 8 µg per kilogram The data for all dose levels in all dogs are summarized in Tables II and III In Fig 2 the dose response curves are shown for the effect of isoproterenol and norepinephrine on contractile

to norepinephrine and isoproterenol may lie at the receptor level or in the ability of the myocardial cell to respond to the consequences of drug receptor interaction

Summary

The inotropic response of the left ventricle to intravenous administration of norepinephrine (NE) and isoproterenol (I) was studied in dogs with congestive heart failure (CHF) resulting from aortocaval fistula Left ventricular contractile force (CF) was recorded at the peak of the length tension curve with a modified Walton Brodie strain gauge arch in five dogs with CHF and five control animals Arterial blood pressure (ABP) and heart rate (HR) were also monitored Graded dose response curves (0 0125 to 1 6 μg per kilogram) were obtained to NE and I The response of CF was significantly depressed at all dose levels to both NE and I in dogs with CHF For example at the dose of 0 8 μg per kilogram the CF response to I in the control dogs was 201 ± 32 per cent above control level whereas in CHF dogs the response was 92 ± 31 5 per cent Similarly NE at this dose level produced a 168 6 ± 14 7 per cent increase in CF in control dogs and 71 ± 21 3 per cent in CHF dogs I was approximately four times as potent as NE and this ratio was not altered in CHF dogs The response of HR and diastolic ABP to drug administration was not altered by CHF These data clearly suggest a depressed inotropic response to β adrenergic stimulation in this CHF model and a separation of the inotropic and chronotropic response

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REFERENCES

1 Chidsey C A Braunwald F Morrow A G and Mason D T Myocardial norepinephrine concentrations in man Effect of reserpine and congestive heart failure N Engl J Med 269 653 1963
2 Chidsey C A Kaiser G A Sonnenblick E H Spann J F and Braunwald E Cardiac norepinephrine stores in experimental heart failure in the dog J Clin Invest 43 2386 1964
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(range 182 to 237) in the control group and 179 (range, 162 to 208) in the CHF group The same dose of isoproterenol produced a heart rate of 237 ± 10 2 (range 218 to 267) in the control group and a heart rate of 253 ± 15 3 (range 209 to 288) in the CHF group

Response of arterial blood pressure to norepinephrine and isoproterenol In the control group carotid artery blood pressure was 149/101 ± 7 3/5 1 mm Hg prior to drug administration In the CHF group carotid pressure was 121/64 ± 15 5/9 1 mm Hg The diastolic blood pressure in the CHF group was significantly lower ($P < 0\ 05$) than in the control group Arterial diastolic blood pressure (ADBP) is reported and used as an index of the influence of the two agonists on the peripheral adrenergic receptor In Tables II and III the response of ADBP and the change in ADBP in response to all doses of norepinephrine and isoproterenol in control and CHF dogs are presented While ADBP was lower in the CHF group there was no significant difference between the control and CHF groups in the change in ADBP produced by any dose of norepinephrine or isoproterenol In control animals 0 8 μg per kilogram of norepinephrine produced a mean increase in ADBP above control of 58 ± 5 8 mm Hg and in the CHF group 50 ± 14 1 mm Hg Isoproterenol 0 8 μg per kilogram produced a mean decrease in ADBP of 59 ± 4 0 mm Hg in control dogs and 37 ± 14 7 mm Hg in CHF dogs Fig 3 shows dose response curves of ADBP and change in ADBP to norepinephrine and isoproterenol in control and CHF dogs

Discussion

From these present experiments we can report the observation that the inotropic response to norepinephrine and isoproterenol is markedly depressed in dogs with CHF whereas the chronotropic and blood pressure response appears to be unaltered When doses of norepinephrine and isoproterenol of 1 6 μg per kilogram were administered to the CHF dogs, the response of left ventricular contractile force was one half and one third, respectively, of that seen in control animals In general the dose response curve for CF was flattened and possibly shifted to the right when compared to normal These findings differ somewhat from those previously published Covell and associates produced heart failure in dogs by inducing tricuspid insufficiency and pulmonary stenosis In these animals the response of right ventricular contractile force to cardioaccelerator nerve stimulation was approximately one half of the response seen in control dogs When norepinephrine, 3 μg per kilogram was administered over a 2 minute period the response of contractile force in heart failure dogs was slightly less than in control dogs but was not significantly different The differences in this previously reported result and those in this present experiment are not precisely determinable However it should be noted that in these present experiments contractile force was recorded from the left ventricle whereas in the report by Covell and associates force was recorded from the right ventricle Further norepinephrine was administered by infusion whereas in our experiments the drugs were given by bolus injection Additionally the alterations in basal myocardial contractile state in response to overload have been shown to vary with the type of load imposed The contractile state of isolated papillary muscle obtained from cats with pressure overload has been shown to be depressed whereas the contractile state of papillary muscles from volume overloaded cats normal The possibility of a varying response to norepinephrine in these two overloaded conditions to our knowledge has not been systematically examined and might account for the difference in response seen in our experiments which are essentially a volume overload model and those of Covell and associates which were pressure overloaded Finally the degree of CHF may influence the results

In these present experiments no data have been developed to aid in defining the mechanism of the depressed contractile force response However it does seem possible to eliminate alteration in systemic hemodynamics as the cause of the response If hemodynamic alterations known to accompany heart failure such as reduced ejection fraction which might tend to dilute the drug injection or altered pulmonary circulation which might delay delivery of the drug from the injection site to the coronary circulation were involved one would expect the response of heart rate and blood pressure to have been reduced also Similarly, alterations in coronary blood flow which might be associated with CHF may possibly be eliminated since the response of heart rate was not depressed If delivery of the drug is unaltered the defect in the contractile response

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investigation combined with the lack of previous data concerning the clinical effects of parasympathomimetic agents in acute myocardial infarction patients without complications were specifically selected who did not exhibit sustained tachyarrhythmias and were hemodynamically stable Thus all patients were classified as Killip Class I or Class II[3] To further reduce the possible risks of adverse sequelae resulting from potent vagomimetic activity no patient was chosen for this study who had electrocardiographic manifestations of intracardiac conduction disorders sinus bradycardia obstructive pulmonary disease or history of peptic ulcer Additionally no patients were selected who had received antiarrhythmic agents digitalis glycosides sympathomimetics or beta adrenergic blocking drugs within 12 hours of the time of the study Further no patients had been administered analgesics within 6 hours of investigation

Hemodynamic assessment The acute hemodynamic effects of edrophonium chloride were evaluated in each of the 11 patients with the Swan Ganz flow-directed catheter Cardiac outputs were obtained in duplicate with the indicator dilution technique Immediately following determination of control values of heart rate systemic arterial pressure pulmonary artery phasic and mean pressures pulmonary artery wedge pressure and cardiac outputs 10 mg of edrophonium chloride were administered intravenously in the following manner the initial 2 mg of the agent were injected over a 30 second period to determine tolerance and then the remaining 8 mg were infused over 1 minute Repeat hemodynamic indices and cardiac outputs were obtained 3 minutes and 10 minutes following the completion of the edrophonium chloride infusion

Antiarrhythmic assessment Continuous electrocardiographic evaluation was carried out in all 11 patients during control and edrophonium chloride administration for a 10 hour period To provide precise determination of each patient s rhythm continuous 10 hour Holter tape monitoring was utilized (Avionics model 400 Electrocardiocorder) At least 30 minutes following the initial 10 mg bolus of the agent given as described initial continuous rhythm monitoring consisted of a 2.5 hour control period in which the patients received no medication Then a 10 mg loading dose of edrophonium chloride was given over 1 minute followed by an infusion of the agent administered at a mean rate of 1 25 mg per minute (range 0.25 to 2 00 mg per minute) for 5 consecutive hours while Holter monitoring was continued Edrophonium chloride was prepared by dissolving 500 mg. in 1 L of dextrose 5 per cent and water and the infusion was carefully regulated by a constant rate infusion apparatus The continuous infusion was given up to a maximum rate of 2 mg per minute or until uncomfortable gastrointestinal symptoms occurred Upon completion of the 5 hours of continuous edrophonium chloride infusion the drug was discontinued and Holter monitoring was continued for an additional 2 5 hour control period during which no medications were given

Qualitative and quantitative analyses of the continuous 10 hour rhythm tapes were accomplished by the high speed 60 1 Avionics Model 660 electrocardioscanner The mean heart rate was determined for each 15 minute period throughout the 10 hours of continuous Holter monitoring All arrhythmias detected by the cardioscanner were recorded on standard electrocardiographic paper for detailed evaluation Premature ventricular contractions were defined as potentially malignant when occurring on the T wave of the preceding QRS complex (R on T phenomenon) when occurring in pairs or multiform in configuration[3] Ventricular tachycardia was defined as three or more premature ventricular contractions occurring in succession at a rate in excess of 120 beats per minute Accelerated idioventricular rhythm was defined as a paroxysmal ventricular rhythm at a rate between 60 and 120 beats per minute

His bundle electrography His bundle electrograms were performed in three patients coincident with the initial hemodynamic studies with an Electronics for Medicine VR 12 recorder Recordings were carried out during the control period immediately preceding the 10 mg bolus of edrophronium chloride and then continuously for 5 minutes following completion of infusion of the agent

Results

Hemodynamic effects The rapid infusion of 10 mg of edrophonium chloride lowered the heart rate 3 minutes following administration in each of the 11 patients from the mean control of 88 ± 6 (S E M.) to 72 ± 4 beats per minutes (b p m) ($p < 0.01$) heart rate returned to predrug values

Clinical evaluation of the enhancement of vagal tone in acute myocardial infarction by edrophonium hydrochloride Effects on ventricular arrhythmias, His bundle electrography, and left ventricular function

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Although it has been the traditional view that increased vagal tone with consequent slowing of heart rate promotes the occurrence of ventricular fibrillation in acute myocardial infarction [1-7] this concept has recently been the subject of considerable controversy [8-11] Thus experimental studies have suggested that vagal stimulation in the presence of acute myocardial ischemia may actually afford protection against re entrant arrhythmias and ventricular fibrillation [11] In contrast previous work has supported the contention that reduced heart rate lowers fibrillation threshold by enhancing the disparity of refractory periods between contiguous regions of myocardium [1-7] Because of the potentially important clinical implications suggested by the experimental observations concerning the antiarrhythmic effect of increased vagal tone upon ischemic heart muscle the present study was undertaken to determine the efficacy of parasympathomimetic stimulation on electrical instability in patients with acute myocardial infarction In the investigation carried out herein, the effect of the parasympathomimetic agent edrophonium chloride were evaluated on cardiac rhythm electrophysiologic properties, and on hemodynamic variables in patients with acute myocardial infarction This study represents the initial clinical evaluation of the possible salutary electrical stabilizing effects observed in the experimental laboratory regarding the protective antiarrhythmic actions of vagal stimulation in acute myocardial ischemia

Materials and methods

The study population was comprised of 11 patients with acute transmural myocardial infarction admitted to the coronary care unit (CCU) of the University of California at Davis-Sacramento Medical Center The investigational protocol was initiated in the immediate period following infarction during the initial 12 hours in the CCU within 24 hours from the onset of symptoms There were nine men and two women, mean age 58 years (39 to 79 years) The diagnosis of acute myocardial infarction was established by the combination of typical clinical history, classic electrocardiographic criteria including pathologic Q waves and enzymatic evidence of myocardial necrosis [12] Six patients had anterior infarctions four had inferior infarctions, and one had combined anterior inferior infarction All patients were in sinus rhythm

Because of the experimental nature of the

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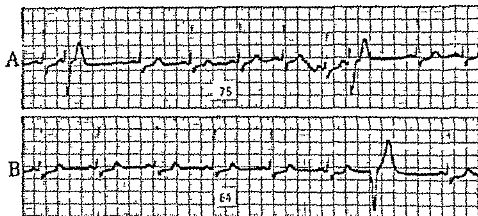


Fig 2 A Control Holter monitor recording of frequent unifocal PVCs occurring on the preceding T wave B Edrophonium infusion 1 5 mg per minute resulted in marked prolongation of the coupling interval between the PVC and preceding QRS complex

over all PVCs was not significantly ($p > 0.05$) altered by edrophonium there was prolongation of the PVC coupling interval in one and emergence of a more benign ectopic focus replacing the early premature beats in the second (Fig 2) resulting in substantial lengthening of the time separating the T wave from the succeeding ventricular ectopic beat Thereby the R on T phenomenon was eliminated in two of the four patients in whom this particular form of serious premature ventricular ectopy occurred

Intracardiac conduction effects The mean control PR interval of 162 ± 7 msec was prolonged to 198 ± 11 msec ($p < 0.01$) 3 minutes following the rapid injection of 10 mg of edrophonium in the 11 patients During the constant 5 hour infusion of edrophonium the average PR segment was lengthened to a lesser extent 176 ± 8 msec ($p < 0.05$) No change ($p > 0.05$) occurred in the QRS duration from the control value of 81 ± 4 msec with the acute or chronic administration of the parasympathomimetic agent

In the patients who underwent His electrography the maximal effect of the rapid 10 mg injection of edrophonium was observed 3 minutes after administration The AH interval was prolonged from 117 ± 4 to 135 ± 7 msec ($p < 0.01$) In contrast parasympathomimetic stimulation changed neither the HQ interval 48 ± 0 8 ($p > 0.05$) nor the QT interval 420 ± 9 ($p > 0.05$)

Side effects No serious adverse effects resulted from the acute or chronic administration of edrophonium in the 11 patients with acute myocardial infarction Seven of the 11 patients experienced transient abdominal discomfort immediately following the 10 mg bolus of the agent, whereas five of the 11 had similar symptoms during the continuous 5 hour infusion which were relieved by minimal reduction in the infusion rate of the drug Three patients developed substantial slowing of sinus rhythm to rates between 45 to 55 bpm during continuous edrophonium administration the heart rate returned to above 60 bpm with reduction in infusion rate and no adverse arrhythmic or hemodynamic effects occurred during the transient bradycardia

Discussion

A slow frequency of cardiac activation as well as ventricular ischemia have been viewed as conditions facilitating temporal dispersion of refractoriness between contiguous areas of myocardium with consequent reduction of fibrillation threshold[1] Accordingly based on these concepts it has been suggested that clinical bradycardia occurring in the presence of myocardial ischemia may result in the unfavorable circumstance provoking re entrant arrhythmias including ventricular fibrillation[5, 9, 18] Furthermore studies in certain experimental preparations have implied that accelerating the rate of stimulation lowers the disparity of refractory periods and increases the threshold for fibrillation[7, 1] It is noteworthy however that the beneficial protective effects of rapid heart rates in limiting temporal dispersion of refractory period and in elevating fibrillation threshold were observed in nonischemic muscle Thus unlike the aforementioned when cardiac rate was escalated in the presence of experimental myocardial ischemia

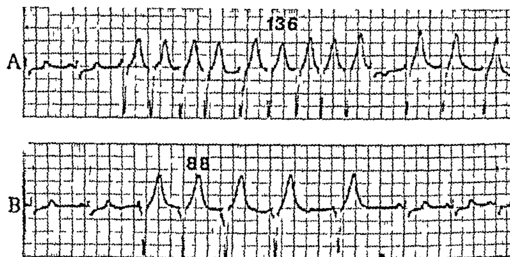


Fig 1 *A* Holter monitor recording of ventricular tachycardia (136 b p m) interrupted by a conducted supraventricular beat and subsequent slower idioventricular rhythm during edrophonium infusion of 0.25 mg per minute *B* With edrophonium infusion rate increased to 0 50 mg per minute the idioventricular rhythm (88 b p m) converted to normal sinus rhythm ventricular tachycardia did not recur

by 10 minutes The average systemic mean arterial pressure of 98 ± 6 mm Hg was unchanged ($p > 0.05$) at both 3 and 10 minutes following the agent Similarly left ventricular filling pressures were unaltered ($p > 0.05$) from the control level of 14 ± 2 mm Hg and the cardiac index was unchanged ($p > 0.05$) from 2 44 L per minute per square meter Coincident with the diminution in heart rate stroke index increased in eight of the 11 patients however the average value for the group was not altered ($p > 0.05$) from the control of 26 ± 3 ml per square meter In addition the stroke work index of 36 ± 3 Gm m /M was not influenced ($p > 0.05$) by the drug

Antiarrhythmic effects Since the electrophysiologic actions of edrophonium during the 5 hour constant infusion period were the same whether compared to the 2 5 hour predrug or 2 5 hour postdrug control periods the results were evaluated by relating the results of the edrophonium infusion to the average values of the combined control phases Nine of the 11 patients demonstrated declines in heart rate with continuous administration of the drug from the mean control rate of 92 ± 4 to 78 ± 6 b p m ($p < 0.01$) The average total number of premature ventricular contractions (PVC's) occurring in the 5 hour control period was 131 ± 51 whereas 138 ± 62 were recorded during the 5 hours of edrophonium infusion ($p > 0.05$) Similarly, the mean number of PVC's per 1,000 beats was 4 7 ± 1 4 in the control phase compared to 5 9 ± 1 2 ($p > 0.05$) during edrophonium

In seven patients (64 per cent) with malignant PVC's in the control period, these serious types of ventricular ectopy was abolished in four individ uals with edrophonium Malignant PVC's ap peared in three additional individuals de p drug infusion thereby six (55 per cent) patie demonstrated serious premature ventri ul beats during edrophonium administratio ($p > 0.05$) Parasympathomimetic stimulati had no over all effect on the frequency of tr sient ventricular tachycardia which was prese in three patients (27 per cent) during the contr period and in four (36 per cent) despite edropho um In the patients with transient ventricul tachycardia accelerated idioventricular rhythm occurred intermittently in two (18 per cent) an three (27 per cent) patients during control an edrophonium infusion, respectively Ventricula fibrillation did not occur during the 10 hou period of study

The interesting phenomenon of abrupt conve sion of ventricular tachycardia to accelerate idioventricular rhythm and consequent return t normal sinus rhythm was observed in tw patients during enhancement of vagal tone wi edrophonium Thus in the representative exampl shown in Fig 1 *A* with infusion of the agent a 0 25 mg per minute ventricular tachycardia (136 b p m was abruptly terminated by a supr ventricular conducted beat with subsequen appearance of a slower idioventricular rhythm With the infusion of edrophonium increased to 0 mg per minute the idioventricular rhyth decreased further in rate and conversion t normal sinus rhythm occurred (Fig 1, *B*) In a additonal two patients in whom the frequency (

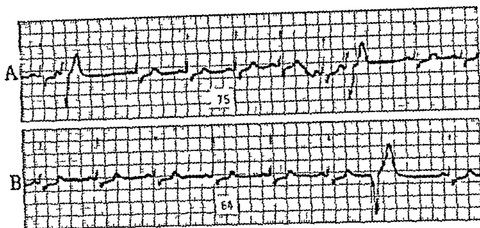


Fig 2 A Control Holter monitor recording of frequent unifocal PVCs occurring on the preceding T wave B Edrophonium infusion 1.5 mg per minute resulted in marked prolongation of the coupling interval between the PVC and preceding QRS complex

overall PVCs was not significantly ($p > 0.05$) altered by edrophonium there was prolongation of the PVC coupling interval in one and emergence of a more benign ectopic focus replacing the early premature beats in the second (Fig 2) resulting in substantial lengthening of the time separating the T wave from the succeeding ventricular ectopic beat Thereby the R on T phenomenon was eliminated in two of the four patients in whom this particular form of serious premature ventricular ectopy occurred

Intracardiac conduction effects The mean control PR interval of 162 ± 7 msec was prolonged to 198 ± 11 msec ($p < 0.01$) 3 minutes following the rapid injection of 10 mg of edrophonium in the 11 patients During the constant 5 hour infusion of edrophonium the average PR segment was lengthened to a lesser extent 176 ± 8 msec ($p < 0.05$) No change ($p > 0.05$) occurred in the QRS duration from the control value of 81 ± 4 msec with the acute or chronic administration of the parasympathomimetic agent

In the patients who underwent His electrography the maximal effect of the rapid 10 mg injection of edrophonium was observed 3 minutes after administration The AH interval was prolonged from 117 ± 4 to 135 ± 7 msec ($p < 0.01$) In contrast parasympathomimetic stimulation changed neither the HQ interval 48 ± 0.8 ($p > 0.05$) nor the QT interval 420 ± 9 ($p > 0.05$)

Side effects No serious adverse effects resulted from the acute or chronic administration of edrophonium in the 11 patients with acute myocardial infarction Seven of the 11 patients experienced transient abdominal discomfort immediately following the 10 mg bolus of the agent whereas five of the 11 had similar symptoms during the continuous 5 hour infusion which were relieved by minimal reduction in the infusion rate of the drug Three patients developed substantial slowing of sinus rhythm to rates between 45 to 55 b p m during continuous edrophonium administration the heart rate returned to above 60 b p m with reduction in infusion rate and no adverse arrhythmic or hemodynamic effects occurred during the transient bradycardia

Discussion

A slow frequency of cardiac activation as well as ventricular ischemia have been viewed as conditions facilitating temporal dispersion of refractoriness between contiguous areas of myocardium with consequent reduction of fibrillation threshold[1] Accordingly based on these concepts it has been suggested that clinical bradycardia occurring in the presence of myocardial ischemia may result in the unfavorable circumstance provoking re entrant arrhythmias including ventricular fibrillation [7, 15, 16] Furthermore studies in certain experimental preparations have implied that accelerating the rate of stimulation lowers the disparity of refractory periods and increases the threshold for fibrillation [4] It is noteworthy however that the beneficial protective effects of rapid heart rates in limiting temporal dispersion of refractory period and in elevating fibrillation threshold were observed in nonischemic muscle Thus unlike the aforementioned when cardiac rate was escalated in the presence of experimental myocardial ischemia

the threshold for ventricular fibrillation has been reported to be reduced in contrast to the decreased predisposition to this lethal arrhythmia noted in the nonischemic heart[10]

Additionally it has been shown experimentally that in the presence of myocardial ischemia the incidence of ventricular ectopic beats may be reduced by bradycardia caused by stimulation of the vagus nerve[8, 11] Moreover enhanced vagal tone per se has been demonstrated to be a salutary phenomenon vs ventricular instability in canine studies in which heart rate was maintained constant thereby suggesting a separate electrical protective action attributable to parasympathetic stimulation alone[8, 11]

The present investigation of the potential antiarrhythmic effects of enhanced vagal tone in acute myocardial infarction extends the previous experimental findings to the clinical setting In the clinical study reported herein it was important that the initial results of the enhancement of parasympathetic activity in acute coronary disease were obtained in patients with relatively stable hemodynamic and electrical properties While it was noted that the over all frequency of serious types of ventricular ectopy were not reduced by the vagomimetic action of edrophonium chloride, nevertheless a number of important salutary effects were observed during infusion of the agent

Thus ventricular tachycardia was terminated in two patients in whom normal sinus rhythm was reestablished following a brief period of less rapid idioventricular rhythm (Fig 1) Concerning the malignant types of premature ventricular contractions these were terminated in four of seven patients by edrophonium while serious PVC s appeared spontaneously in three individuals despite vagal tone enhancement Furthermore, edrophonium was associated with prolongation of the coupling interval between PVC s and the antecedent sinus beats in two of the four patients exhibiting the R on T phenomenon consequently abolishing malignant PVC s in both of these individuals Therefore potentially lethal tachyarrhythmias (malignant PVC s or ventricular tachycardia) were terminated in six of 10 patients by edrophonium However it should be pointed out that serious arrhythmias not present in the control period appeared in four patients despite drug administration and were not abolished by increased parasympathomimetic activity in these individuals

Pertinent to the antiarrhythmic effects of enhanced vagal tone are the electrophysiol[...] studies carried out by Fisch and Bailey and th[...] associates[17, 18] in canine heart muscle Th[...] investigators demonstrated that acetylchol[...] shortens repolarization of the proximal H[...] Purkinje system as well as increases intracell[...] negativity during diastole thereby resulting in greater responsiveness with consequent accele[...]tion of conduction velocity These importa[...] parasympathomimetic induced alterations of th[...] His Purkinje specialized conduction system a[...]tenuate the electrophysiologic milieu pred[...]posing to re entrant ventricular tachyarrhyth[...]mias In addition ischemia provoked heteroge[...]ity of excitability, a principal determinant o[...] reciprocal excitation is reduced as well as th[...] appearance of ectopic automaticity is de[...]pressed [3] Further, experimental studies by Sas[...]wicz and co workers[19] have demonstrated tha[...] the initiation of ventricular fibrillation is enhanced by slowed ventricular conduction of the first propagated premature beat after electrical stimulation this deleterious effect would be anticipated to be counteracted by increased parasympathomimetic activity [...] Moreover Crane[...]field and co workers[20] have delineated a slow response arising from partially depolarized Pu[...]kinje fibers with markedly depressed conduction velocity and prolonged refractory period which is prone to block at branch points in the conduction pathways Since localized ischemia induce[...] partial depolarization resulting in slow depolari[...]zation responses increasing the likelihood of re[...]entrant arrhythmias acetylcholine and thereby elevated vagal tone would be expected to favor[...]ably alter the action potential in a manner inhib[...]iting the initiation of such slow responses

In regard to the absence of adverse hemody[...]namic actions of edrophonium shown in this clinical investigation experimental studies have indicated that two distinct cholinergic receptors for acetylcholine may exist in cardiac tissue one located at vagal nerve endings responsive to direct parasympathetic nervous stimulation which mediates a negative inotropic effect while the second receptor is situated distal to nerve endings which exerts a mild positive inotropic action upon humoral activation[21] Although studies in intact dogs have shown a mild negative ventricular contractile response with direct vagal nerve stimulation[22, 23] apparently through activa[...]tion of receptor one of the minimal parasympa[...]

ic innervation of the ventricles,[4] the lack of ...ession of cardiac function with edrophonium ...e patients evaluated herein appears to be the ...lt of the drug being able to affect only the ...se type two acetylcholine receptors in ven...ular myocardium.

...n the present clinical investigation significant ...lines in heart rate were produced by both the ...idly administered bolus of edrophonium as ...l as the slow continuous infusion of the agent. ...ce heart rate is a principal determinant of ...ocardial oxygen consumption[2] and augmenta...n of heart rate worsens the extent of ischemic ...ury in coronary disease,[2] controlled slowing ...the frequency of contraction in patients with ...ite myocardial infarction may afford limita...n of the ischemic area and thereby restrict ...ssible sites of reentrant electrical irritability. ...hus, although in nonischemic experimental ...nditions acceleration of heart rate may atte...iate the electrical properties promoting re...trant arrhythmias, mitigation of ischemia by ...owing heart rate may offset the potential ...lverse electrophysiologic consequences of re...iced heart rate per se. It has also been observed ...perimentally that vagal stimulation may ...roduce coronary artery dilation independent of ...arasympathetic mediated chronotropic and ino...ropic actions, thereby providing an additional ...otential mechanism for modifying myocardial ...chemia. Furthermore, acceleration of heart rate ...y atropine has been shown to be ineffective in ...meliorating experimental ischemic induced ar...hythmias, and clinical atropine induced tachy...cardia has provoked ventricular ectopy, and even ...precipitated ventricular fibrillation.

The present investigation assesses for the first ...ime the clinical effects of increased vagal tone on ...ntracardiac conduction intervals in the setting of acute myocardial infarction. It was observed that edrophonium effected prolongation of A-H conduction time but did not delay the H-V conduction interval. However, it should be pointed out that patients with infra His bundle conduction abnormalities were specifically not selected for study. Nevertheless, the present findings indicate that stimulation of the normal His-Purkinje system does not produce alterations in conduction velocity in these specialized fibers.

The present investigation represents the initial experience in the application to patients with acute myocardial infarction the concepts derived from recently described experimental observations concerning the effects of vagal stimulation in acute coronary ligation.[11] The clinical data herein indicate that the frequency of ventricular ectopic beats are not significantly altered and that the appearance of potentially malignant forms of PVC's and the occurrence of ventricular tachycardia are not completely prevented by increased vagomimetic activity. In certain patients with acute coronary disease, however, the malignant character of frequent premature ventricular contractions and even ventricular tachycardia itself may be reduced by parasympathomimetic stimulation with edrophonium. Importantly, edrophonium infusion resulted in no adverse hemodynamic effects in patients with acute myocardial necrosis. Because of the caution necessarily exercised in the selection of patients for this initial controlled trial of parasympathomimetic therapy in clinical myocardial infarction, high risk unstable coronary patients with frequent malignant ectopy and recurrent ventricular tachyarrhythmias and ventricular fibrillation were not chosen for study. Therefore, the possibility exists that additional beneficial effects may be possible in acute ischemic heart disease with greater electrical instability.

Summary

Enhanced electrical stability of acutely ischemic myocardium with vagal stimulation and acetylcholinesterase inhibition has been demonstrated experimentally. To extend these findings clinically, within 24 hours of acute myocardial infarction 11 patients underwent continuous 10 hour Holter monitoring: 2.5 hour control before and after 5 hour constant edrophonium infusion (0.25 to 2.00 mg./minute). Continuous infusion of the agent lowered heart rate 92 to 78 b.p.m. ($p < 0.01$). Although mean total ventricular extrasystoles (PVC's) per 5 hours per patient (131) and PVC's per 1,000 beats (4.7) were unchanged ($p > 0.05$), potentially lethal tachyarrhythmias (malignant PVC's: multifocal, R on T, paired, >5 per minute or ventricular tachycardia) were terminated in six of 10 patients by edrophonium. However, serious ventricular arrhythmias continued in three patients and appeared in four despite the agent. Ventricular fibrillation did not occur during the 10 hour period of study. In addition, the patients were evaluated hemodynamically and by His bundle electrograms before and after a 10 mg. bolus of edrophonium prior to the 10 hour constant infu-

sion heart rate declined (88 to 72 bpm p < 0 01) while mean arterial pressure (98 mm Hg) left ventricular filling pressure (14 mm Hg), cardiac index (2 4 L per minute per square meter) and stroke work index (36 Gm m /M²) were unchanged (p > 0 05) The edrophonium bolus prolonged the A H interval (117 to 135 msec p < 0 01) while the H Q interval was unaltered (48 msec p > 0 05) It is concluded that increased vagal tone with edrophonium did not reduce the over all presence of premature ventricular contractions in the entire study group however the malignant nature of PVC s and ventricular tachycardia appeared to be lessened by the parasympathomimetic agent in certain patients In addition no adverse hemodynamic or intraventricular conduction effects were produced by edrophonium administration

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REFERENCES

1. Kerzner J Wolf M Kosowsky B D and Lown B Ventricular ectopic rhythms following vagal stimulation in dogs with acute myocardial infarction Circulation 47 44 1973
2. Cranefield P F Ventricular fibrillation N Engl J Med 289 732 1973
3. Han J The concepts of re entrant activity responsible for ectopic rhythms Am J Cardiol 28 253 1971
4. Han J Ventricular vulnerability during acute coronary occlusion Am J Cardiol 24 857 1969
5. Han J Mechanisms of ventricular arrhythmias associated with myocardial infarction Am J Cardiol 24 800 1969
6. Lown B Fakhro A M Hood W B and Thorn G W The coronary care unit J A M A 199 188 1967
7. Han J Millet D Chizzonitti B and Moe G K Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate AM HEART J 71 481 1966
8. Myers R W Pearlman A S Hyman R M Goldstein R A Kent K M Goldstein R F and Epstein S E Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia Circulation 49 943 1974
9. Goldstein R E Karsh R B Smith E R Orland M Norman D Farnham G Redwood D R and Epstein S E The influence of atropine and of vagally mediated bradycardia on the occurrence of ventricular arrhythmias following acute coronary occlusion in closed chest dogs Circulation 47 1180 1973
10. Kent K M Smith E R Redwood D R and Epstein S E Electrical stability of acutely ischemic myocardium Influences of heart rate and vagal stimulation Circulation 47 291 1973
11. Corr P B and Gillis R A Role of the vagus nerves in the cardiovascular changes induced by coronary occlusion Circulation 49 86 1974
12. Sobel B E and Shell W E Serum enzyme determinations in the diagnosis and assessment of myocardial infarction Circulation 45 471 1972
13. Killip T and Kimball J T Treatment of myo infarction in a coronary care unit Am J Cardiol 2? 1967
14. Vismara L A Amsterdam E A and Mason, D Relation of ventricular arrhythmias in the late h? phase of acute myocardial infarction to sud? d? after hospital discharge Am J Med 59 6 19?
15. Webb S W Adgey A A J and Pantrid J Autonomic disturbances at onset of acute myo? infarction Br Med J 3 89 1972
16. Zipes D P The clinical significance of brady? rhythms in acute myocardial infarction Am J C? 24 814 1969
17. Fisch C Knoebel S B and Feigenbaum H The? of acetylcholine and potassium on repolarizatio of heart J Clin Invest 43 1769 1964
18. Bailey J C., Greenspan K Elizari, M V Ande? G J and Fisch C Effects of acetylcholine on a? ticity and conduction in the proximal portion of the Purkinje specialized conduction system of the d g C Res 30 210 1972
19. Surawicz B Gettes L S and Ponce Z ? Relation of vulnerability to ECG and action p? characteristic of premature beats Am J Phy? 212 1519 1967
20. Cranefield P F Wit A L and Hoffman B F Conduction of the cardiac impulse III Characteristi? very slow conduction J Gen Physiol 59 ?? 19?
21. Buccino R A Sonnenblick E H Cooper T ? Braunwald E Direct positive inotropic effect of ? choline on myocardium Evidence for multiple ch? ergic receptors in the heart Circ Res 19 109 1?
22. Daggett W M Nugent G C Carr P W Powers, P C and Harada Y Influence of vagal stimulatio? ventricular contractility O consumption and cor? flow Am J Physiol 212 8 1967
23. DeGeest H Levy M N Zieske H and Lipman R L Depression of ventricular contractility by stimulati? of the vagus nerves Circ Res 17 222 1965
24. Jacobowitz D Cooper T and Barner H B H? chemical and chemical studies of the localization of adrenergic and cholinergic nerves in normal and de? vated cat hearts (abst) Fed Proc 25 383 1966
25. Braunwald E Control of myocardial oxygen consump tion Physiologic and clinical considerations Am J Cardiol 27 416 1971
26. Redwood D R Smith E R and Epstein S E Coronary artery occlusion in the conscious do Effec of alterations in heart rate and arterial pressure on the degree of myocardial ischemia Circulation 46 ?? 1972
27. Maroko P R Kjekshus J K Sobel B E Watanabe T Covell J W Ross J and Braunwald E Factor influencing infarct size following experimental corona? artery occlusion Circulation 43 67 1971
28. Feigl E O Parasympathetic control of coronary blood flow in dogs Circ Res 25 509 1969
29. Karsh R B Orlando M Norman D and Epstein S E Ineffectiveness of prophylactic atropine ? decreasing arrhythmias and enhancing survival followi? acute coronary artery occlusion in conscious dogs (abs? Am J Cardiol 29 273 1972
30. Zipes D P and Knoebel S B Rapid rate-dependent ventricular ectopy Adverse responses to atropine induced rate increase Chest 62 255 1972
31. Massumi R A Mason D T Amsterdam E A DeMaria A N Miller R R Scheinman M M and Zelis R Ventricular fibrillation and tachycardia after intravenous atropine for treatment of bradycardia N Engl J Med 287 336 1972

-termittent parasystole with concealed extrasystolic -geminy during myocardial infarction

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tana Calif

rmittent parasystole (IP) is a rare arrhythm with few unequivocal reported cases The inguishing feature of continuous parasystole uninterrupted entrance block into the ectopic cemaker IP is thought to occur when there is mporary failure of entrance block with reset ıg of the parasystolic cycle length[2]

Concealed extrasystolic bigeminy is a disorder r rhythm in which a coupled persistent and ontinuous ectopic mechanism is present but xtrasystoles often do not become manifest ecause of a presumed exit block

This communication reports the coexistence of hese two unusual rhythms during acute myocar ıal infarction (MI)

ase report

A 72 year-old man with a history of an antecedent anterior all MI 13 years previously and new accelerated angina was dmitted with severe oppressive chest pain of several hours uration. Serial electrocardiograms (ECG) and serum enzyme leterminations demonstrated the evolution of a transmural nferior wall MI IP appeared on the fourth hospital day ersisted for 6 days and then disappeared The patient did not levelop shock congestive heart failure or other significant arrhythmias he was discharged asymptomatic after 3 weeks of hospitalization

Results

Fig 1 demonstrates conducted and ectopic parasystolic beats Conducted beats have a P R interval of 0 24 sec are wide with a superior frontal axis and show anterior and inferior wall MI patterns A vectorcardiogram confirmed both MI s as well as atypical left bundle branch block (LBBB) Ectopic beats are much wider and notched have a frontal axis similar to conducted beats and have a LBBB configuration

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Fig 2 shows uninterrupted selections (Panels *A* and *B*) from two separate continuous recordings obtained 24 hours apart Each recording demon strated a similar allorhythmia diagnostic of IP Table I summarizes all pertinent intervals measured from the recordings

During both recordings P P intervals are rela tively constant and vary from 0 92 to 0 97 sec with a mean of 0 945 sec Unifocal ectopic beats occur in series have interectopic intervals of 1 64 to 1 88 sec and usually demonstrate successively shorter coupling intervals to preceding conducted beats because the interectopic intervals are slightly shorter than two sinus cycles (1 84 to 1 94 sec) Coupling intervals vary widely from 0 48 to 0 96 sec a hallmark of parasystole The 1st ectopic beat of each parasystolic series is often a fusion beat and is always coupled to its second preceding conducted beat These coupling inter vals (1 74 to 1 92 sec) are always shorter than the two previous P P intervals Successive interec topic intervals in a series tend to slightly shorten with the last parasystolic cycle usually being the shortest in the series However there is sometimes slight lengthening in successive intervals (0 02 to 0 04 sec)

Although sinus node intervals were similar in both recordings interectopic intervals were usually longer in the second recording There was also less of a tendency for successive parasystolic cycle lengths to shorten in the second recording There were also consistently four or five succes sive cycles in each parasystolic series during the second recording in contrast to the usual three in the first recording

The intervals between the last ectopic beat of a parasystolic series and the 1st beat of the next series (either a pure ectopic or a fusion beat) were never multiples of the parasystolic cycle length Instead the first beat always demonstrated rela tively fixed coupling to its second preceding

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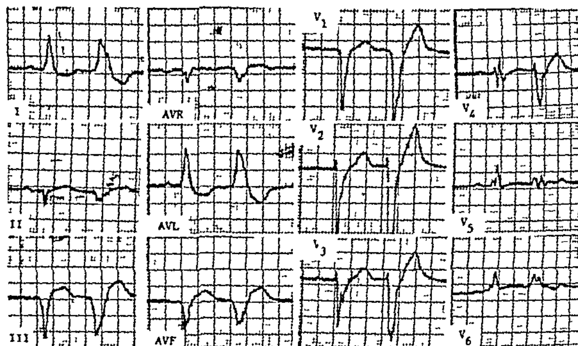


Fig 1 Simultaneous three lead recordings In each lead the first beat is a conducted beat and the second beat is a parasystolic beat

Table I Interectopic and coupling intervals (intervals in hundredths of a second)

First cycle	*Second cycle*	*Third cycle*	*Fourth cycle*	*Fifth cycle*	*Intervening conducted beats*
First recording					
180 (102)	(76) 178 (116)	(59) 175 (133)			4
181 (103)	(74) 177 (114)	(60) 174 (132)			6
178 (100)	(71) 171 (114)	(58) 172 (126)			6
179F (97)	(79) 176 (106)	(64) 170 (124)			6
181 (100)	(74) 174 (114)	(58) 172 (128)			4
174 (103)	(70) 173 (120)	(48) 168I (140)			5I
181 (105)	(72) 177 (120)	(51) 171 (143)			4
177 (112)	(64) 176 (129)				4
190F (99)	(79) 178 (114)	(58) 172 (133)			4
176 (108)	(68) 176 (118)	(46) 164I (142)			5I
176 (104)	(70) 174 (118)	(48) 166I (142)			5I
185F (97)	(78) 175 (108)	(66) 174 (126)			6
176 (110)	(66) 176 (124)				–
Mean 179 5	175 5	170 7			
Second recording					
184 (99)	(81) 180 (107)	(73) 180 (118)	(61) 179 (126)		18
188F (100)	(84) 184 (106)	(72) 178 (118)	(61) 179 (129)		6
186F (94)	(86) 180 (101)	(77) 178 (112)	(66) 178 (117)	(48) 165 (138)	2?
185 (97)	(80) 177 (105)	(74) 179 (114)	(54) 168 (131)		6
185F (100)	(82) 182 (110)	(72) 182 (118)	(52) 170 (138)		4
186F (99)	(84) 183 (104)	(78) 182 (107)	(76) 183 (120)	(56) 176 (130)	10
187 (98)	(82) 180 (110)	(72) 182 (120)	(54) 174 (139)		6
185 (100)	(83) 183 (112)	(71) 183 (122)	(58) 180 (135)		8
189F (100)	(84) 184 (108)	(75) 183 (117)	(64) 181 (129)		10
192F (99)	(89) 188 (104)	(84) 188 (109)	(72) 181 (118)	(65) 183 (127)	12
190F (100)	(88) 188 (106)	(76) 182 (118)	(65) 183 (128)		–
Mean 187 0	182 6	181 5	177 8	174 7	

Intervals without parentheses are parasystolic cycle lengths The first cycle interval is actually a coupling interval to a conducted beat The interval in parentheses on the right in each column is the interval from a parasystolic beat to the following conducted beat while the interval in parentheses on the left is the coupling interval to the preceding conducted beat F = fusion beat I = interpolated beat

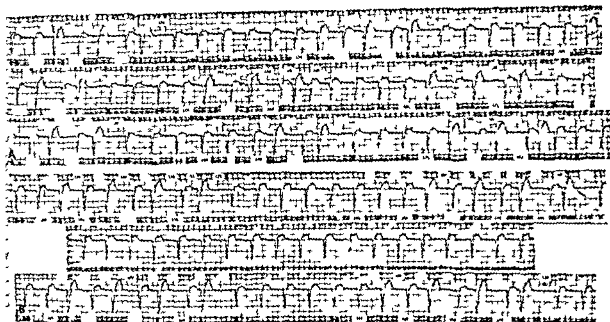


Fig 2 A First recording B second recording All intervals in hundredths of a second Top intervals are coupling intervals between successive beats either conducted or parasystolic. Bottom intervals are parasystolic interectopic intervals. The first interval in each parasystolic series is actually the coupling interval to the second preceding conducted beat Note the critical interval of 1 24 sec after an ectopic beat causing entrance block failure the even number f sinus beats between parasystolic series except after interpolated ectopic beats (odd number) and less aberrant QRS complexes at an interval of 1 08 sec or more after an ectopic beat F = fusion beat I = interpolated beat arrow start of each parasystolic sequenc x conducted beat interrupting parasystolic entrance block

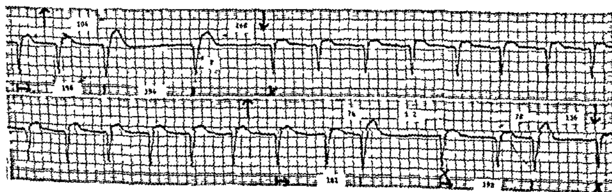


Fig 3 Intervals and symbols as in Fig 2 ↑ start of carotid sinus massage ↓ end of carotid sinus massage

conducted beat with this coupling interval approximating or being slightly longer than the following parasystolic cycle lengths This behavior fulfills the characteristic features of IP [1]

The termination of each parasystolic series was related to a critical interval between its ectopic beats and the following conducted beats In 60 instances these intervals varied from 0 94 to 1 22 sec and the parasystolic rhythm continued uninterrupted with the next expected parasystolic beat appearing on time However the parasystolic rhythm was terminated (became intermittent) in all 24 instances when this interval ranged from 1 24 to 1 43 sec In the first recording period there were three instances of interpolated parasystolic beats with intervals of 0 60 to 0 62 sec between ectopic beats and the subsequent conducted beats The intervals between these interpolated beats and the following second conducted beats were the longest observed (1 40 to 1 43 sec) and always terminated the parasystolic series The above findings indicate that the refractory period of the parasystolic focus's protection from conducted beats (duration of

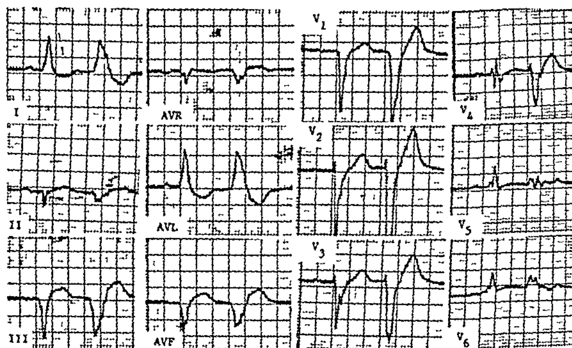


Fig 1 Simultaneous three lead recordings In each lead the first beat is a conducted beat and the second beat is a parasystolic beat

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174 (103)	(70) 173 (120)	(48) 168I (140)			5I
181 (105)	(72) 177 (120)	(51) 171 (143)			4
177 (112)	(64) 176 (129)				4
190F (93)	(79) 178 (114)	(58) 172 (133)			4
176 (108)	(68) 176 (118)	(46) 164I (142)			5I
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185F (97)	(78) 175 (108)	(66) 174 (126)			6
176 (110)	(v6) 176 (124)				–
Mean 179 5	175 5	170 7			
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186F (94)	(86) 180 (101)	(77) 178 (112)	(66) 178 (117)	(48) 165 (138)	22
185 (97)	(80) 177 (105)	(74) 179 (114)	(54) 168 (131)		6
185F (100)	(82) 182 (110)	(72) 182 (118)	(52) 170 (138)		4
186F (99)	(84) 183 (104)	(78) 182 (107)	(76) 183 (120)	(56) 176 (130)	10
187 (98)	(82) 180 (110)	(72) 182 (120)	(54) 174 (139)		6
185 (100)	(83) 183 (112)	(71) 183 (122)	(58) 180 (13.)		8
189F (100)	(84) 184 (108)	(75) 183 (117)	(64) 181 (129)		10
192F (99)	(89) 188 (104)	(84) 188 (109)	(72) 181 (118)	(65) 183 (127)	12
190F (100)	(88) 188 (106)	(76) 182 (118)	(65) 183 (128)		–
Mean 187 0	182 6	181 5	177 8	174 7	

Intervals without parentheses are parasystolic cycle lengths The first cycle interval is actually a coupling interval to a conducted beat. The interval parentheses on the right in each column is the interval from a parasystolic beat to the following conducted beat while the interval in parentheses on the left is the coupling interval to the preceding conducted beat F = fusion beat I = interpolated beat

ic series This coupling interval was either ual to or slightly longer than subsequent cycle igths in the same series

Kinoshita has recently reported two separate ses of IP One case[4] showed consistent failure of trance block at an interval of 0 76 sec after a rasystolic beat The coupling interval between e first parasystolic beat in a series and the nducted beat terminating entrance block was ways slightly longer than the uninterrupted arasystolic cycle length The other case[5] demon rated a complex arrhythmia with a sinus beat enetrating into the entrance block of the para ystolic focus at an interval of 1 12 to 1 30 sec in a Mobitz type I fashion

This present case of IP is similar in many espects to previously reported cases but also ifferent in several aspects

The parasystolic rate tended to slightly accel rate during each series with the initial coupling nterval i.e the first parasystolic cycle length sually being the longest and with the last cycle ength (immediately preceding entrance block ailure) usually being the shortest This initial engthening could have been caused by conduc ion delay of the sinus impulse into the parasys olic site or by transient depression of the para systolic focus by this sinus impulse[2] with a subse quent "warming up and acceleration as is often observed in ectopic rhythms

In this case as in previous reports[2,4] the first beat in each parasystolic series was coupled to its second preceding conducted beat A unique feature however was the finding that the first ectopic beat was never coupled to the first conducted beat in each series (the beat termi nating entrance block) but rather to the third conducted beat or some other successive odd number beat In contrast other reports have always shown coupling of the first ectopic beat to the first conducted beat of the parasystolic sequence An explanation for this unusual behavior might be initial lengthening of the first cycle because of either conduction delay or tran sient suppression If this cycle length were greater than 1 84 to 1 94 sec (two P P intervals) the first parasystolic beat would fall on or after the third conducted beat and would not become manifest because of temporary ventricular refractoriness The next parasystolic beat with a shorter cycle length would become manifest after the fourth conducted beat and would appear to be coupled to the third conducted beat

Fig 3 shows the effect of carotid sinus massage on IP with both sinus slowing and A V block The first two parasystolic beats do not have an inter vening conducted beat and have a long ectopic cycle length of 1 94 sec Entrance block failure then occurs and 16 conducted beats (an even number) intervene between the second and third ectopic beats Entrance block failure again occurs and the fourth ectopic beat is now coupled to the first conducted beat after this failure at a long interval of 1 98 sec All ectopic beats in this recording except the third one would have been concealed or recycled if the sinus rate had not been slowed The coupling interval of 1 98 sec might represent the true initial concealed para systolic cycle length although carotid sinus massage by itself can slow parasystole

A second although less tenable mechanism for the gradual cycle length shortening in each series with a subsequent pause could be a Mobitz type I exit block from the parasystolic focus This would explain the delay of a parasystolic beat until after the fourth conducted beat However Wencke bach periodicity usually causes a more dramatic shortening of R R intervals Moreover the termi nation of each parasystolic series was always related to a critical interval of $>1\ 22$ sec This finding would favor entrance block failure rather than exit block as a mechanism for intermit tency

The demonstration of a concealed bigeminal rhythm before the appearance of parasystole has not been reported previously in true IP The explanation for this phenomenon is also specula tive If the initial parasystolic cycle length was considerably lengthened to more than two P P intervals every other conducted beat could continuously penetrate and reset the parasystolic focus with its eventual appearance occurring first as a concealed beat because of ventricular refrac toriness (see above) and then as a manifest beat Table I reveals that during the second recording parasystolic cycle lengths were usually longer than those in the first recording and were usually associated with much longer periods of conceal ment i e 22 18 12 etc uninterrupted con ducted beats This association of longer cycle lengths and perhaps even longer initial cycle lengths with longer periods of concealment would

entrance block) is 1 22 sec Thus the parasystolic pacemaker exhibits entrance block and possesses protection from sinus impulses for 1 22 sec of its ~1 80 sec cycle length If a conducted beat occurs after this 1 22 sec refractory period, the parasystolic focus demonstrates failure of entrance block with loss of protection and resetting of its cycle length

Parasystolic series in the second recording always contained more ectopic beats than those in the first recording The mechanism for this finding were the longer parasystolic cycle lengths observed in this recording which more approximated two P-P intervals This resulted in longer coupling intervals to preceding conducted beats, and consequently shorter intervals to following conducted beats Thus it took longer in this recording to reach the interval of 1 24 sec required to terminate parasystole

Conducted beats showed different degrees of aberration relative to their intervals to preceding ectopic beats Intervals of 1 08 sec or more resulted in beats with a narrower QRS complex and a less elevated T wave (Fig 2)

The number of conducted beats intervening between parasystolic series demonstrated an interesting phenomenon (last column, Table I) In all instances without interpolation, there was always an even number of these beats ranging from 4 to 22 This would suggest concealed extrasystolic ventricular bigeminy [5, 6] However, in this arrhythmia, only an odd number of conducted beats are observed between extrasystoles, conforming to the formula $2n + 1$ [6] This discrepancy can be explained by the fact that the first parasystolic beat of each series (actually a forced extrasystole) is coupled to its second preceding conducted beat rather than to its immediately preceding conducted beat as is usually the case in ventricular bigeminy Thus the formula becomes $2n + 2$, an even number The only exceptions to this even number distribution occurred after each interpolated parasystolic beat when odd numbers of conducted beats intervened between parasystolic series (5, 5, 7) This discrepancy can be explained by the fact that compensatory pauses do not follow interpolated extrasystoles and an extra conducted beat has to be added to the number of beats between interectopic intervals [7] The formula thus becomes $2n + 3$, an odd number

Analysis of the R R intervals of conducted beats intervening between the last and first ectopic beat of successive parasystolic series did not demonstrate any relationship between these intervals and the appearance of manifest extrasystoles or the nonappearance of concealed extrasystoles [7]

Discussion

Ventricular parasystole is a unique arrhythmia in which an ectopic pacemaker develops complete entrance block and protection against other dominant faster pacemakers It is characterized by mathematically related interectopic intervals variable coupling to conducted beats and frequently ventricular fusion complexes Intermittent ventricular parasystole is less common and occurs when the ectopic focus possesses incomplete protection with temporary failure of entrance block when challenged by a conducted beat This temporary failure usually occurs late in the parasystolic cycle length and results in resetting of the parasystolic impulse

Schamroth and Marriott[5, 6] have reported several cases of a form of IP with alternating parasystolic and extrasystolic rhythms from the same ectopic focus Long sequences of a manifest extrasystolic bigeminy with fixed coupling intervened between parasystolic sequences These authors however did not comment on the mechanism causing the disappearance of entrance block and attributed this alternation to ectopic enhancement of the extrasystolic beat by Wedensky facilitation

Steffens[1] in 1971 reported a case of IP and attributed its intermittency to failure of entrance block after parasystolic beats

Cohen Langendorf and Pick[2] reported 10 cases of IP all of which demonstrated a similar mechanism to explain entrance block failure Eight cases showed early protection in the parasystolic cycle with a loss of protection at a predictable cut off interval later in the cycle length Two cases interestingly only showed protection late in the parasystolic cycle In all 10 cases after failure of entrance block with discharge and resetting of the parasystolic cycle, the first ectopic beat of each parasystolic series exhibited a constant coupling interval to its second preceding sinus beat This same sinus beat was also always the beat which had interrupted the previous parasys

ardiac arrhythmias on swallowing

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ardiac arrhythmias on swallowing is a rare but troublesome disorder which usually presents as yncopal attacks or palpitations associated with he ingestion of food or drink A functional esophageal disorder such as incoordinate peristal ic activity synonyms being corkscrew esopha gus or diffuse esophageal spasm is by far the commonest recognizable cause of swallow syn ope[1] The esophageal diverticula which were thought to be the cause of syncope in some of the earlier case reports[3] may well have been second ary to incoordinate peristaltic activity of the esophagus Swallow syncope has been associated with demyelination of the vagus nerve and infil tration of the glossopharyngeal nerve by meta static carcinoma of the lung and has been reported to be the presenting symptom of a patient with adenocarcinoma of the lower third of the esophagus

Disorders of cardiac rhythm responsible for this phenomenon of swallow syncope in the reported cases are various degrees of atrioventricular block nodal or sinus bradycardia ventricular asystole and atrial fibrillation We report a patient who suffered from troublesome cardiac arrhythmias as a result of incoordinate peristaltic contractions of the esophagus on swallowing

Case history

A. T a 4b-year-old active man was first seen in January 19?? with a 4 *months* history of dizziness and palpitation on swallowing These symptoms were brought on more by sol d food than liquids These episodes were steadily getting more frequent and at the time of admission were regular events whenever *he* swallowed food or drink The duration of these episodes was approximately .0 seconds and reco ery was *rapid* once he had finished swallowing He never went completely unconscious There was no history of ischemic heart disease His blood pressure was 130/80 mm Hg and his pulse was regular with a rate of 80 per minute Physical examination was normal and so were hematological and biochemical profiles and a chest x ray Repeated urinary catecholamines were normal A root and arch aortogram was performed to *exclude* an intrathoracic secreting tumor such as a pheochromocy toma. The electrocardiogram showed normal sinus rhythm but on eating a meal runs of atrial fibrillation ventricular tachycardia and supraventricular tachycardia (Figs 1A and *1B*) unaffected by intravenous phenytoin lignocaine or carotid sinus massage were observed Barium swallow exami nation did not reveal a hiatal hernia or gastroesophageal reflux Incoordinate peristaltic contractions were present in the lower half of the esophagus The esophageal motility was poor and clearance of swallowed barium slow The first peristaltic wave came in ?0 second after swallowing and was weak the clearance was almost complete in 60 *seconds* Barium by itself did not reproduce the arrhythmias but swallowing barium with apple readily produced the arrhythmias. At esophagoscopy the esophagus *appeared* normal Esophageal manometry showed nonprogressive and incoordinated peristaltic contractions Balloon distension of *the esopha*?u reproduced the arrhythmias between 30 and 38 cm from the anterior nares Infusion of *N*/10 HCl *into* the lower third of the esophagus did not *produce* any arrhythmias

Although these arrhythmias were easy to *reproduce in* the conscious state anesthesia with sodium Pentothal and nitrous oxide and oxygen completely abolished the reflex and all attempts to reproduce these *abnormal rhythms* on the operat ing table were futile Hence the actual area where d nervation was to be effected *was difficult* to pinpoint accurately but preoperative testing had indicated the reflexes to be arising predominantly from the lower third of the esophagus Hence an operative plan to interrupt *the local* nerve plexuses by doing a circular myotomy down to the mucosa at the junction of the middle third and *the lower* third was adopted and carried out During surgery extrasystoles associated with a fall in blood pressure *did occur* but this could not be pinpointed to any particular event *and was not* troublesome The esophagus appeared normal on naked-eye examination

In the *immediate* postoperative period the patient complained of dysphagia for fluids and solids and a barium swallow revealed distension of the mucosa at the area of the myotomy and an initial delay in *emptying* of the stomach

Prior to surgical treatment he obtained partial relief of his

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tend to support this hypothesis Theoretically, if twice the sinus cycle became shorter than the parasystolic cycle length, no ectopic beats would be seen This finding has been confirmed by Kinoshita and Tanabe[4]

IP is rarely observed during MI, although three of the 10 cases of Cohen, Langendorf, and Pick[2] apparently had an acute MI

Salazar and McKendrick[8] found 11 cases of parasystole in 630 consecutive MI's an incidence of 1 7 per cent Only two of these 11 cases demonstrated true IP, an incidence of 0 3 per cent

Baxter and McGuinness[9] reported 15 cases of ventricular parasystole in 369 MI s an incidence of 4 1 per cent In most of these 15 cases parasys tolic beats appeared intermittently This how ever, was caused by a degree of exit block and was not true intermittent parasystole, since interval measurements between episodes of ectopic rhythm were multiples of the basic ectopic para systolic cycle length

Acute MI and necrosis can produce enhanced ventricular automaticity and slow unidirectional conduction an ideal setting for either continuous or intermittent parasystole[10]

Lightfoot[11] has reported a case of acute inferior wall MI with ventricular parasystole This patient s ectopic beats had a right bundle branch block and left axis deviation configuration as would be expected from a focus in the left ventric ular inferior wall

The case in this communication, however demonstrated ectopic beats with a LBBB and left axis deviation configuration (Fig 1) A fascicular or an A V junctional focus with aberration cannot be excluded as the origin of this rhythm Late diastolic beats arising from an eccentric part of the A V junction can exhibit both aberration and fusion with conducted impulses[12] His bundle electrogram studies have established the unequiv ocal A V junctional origin of a continuous para systolic rhythm with aberration[13] His bundle recordings have also shown that an intermittent parasystolic focus with wide QRS complexes was located in the fascicular system Thus His bundle studies are needed to differentiate ventricular from superventricular parasystolic rhythms ei ther continuous or intermittent

Summary

A 72 year old man demonstrated per intermittent ventricular parasystole for 6 d during an acute inferior wall myocardial in tion Entrance block failure occurred at a cr interval of 1 24 sec after parasystolic beats resetting of the parasystolic cycle length T first ectopic beat in each parasystolic s showed coupling to its second preceding c ducted beat and successive cycle lengths in series usually showed gradual shortening Co cealed extrasystolic bigeminy was also dem strated between parasystolic series with t number of intervening conducted beats co form ing to the formula $2n + 2$ After interpol parasystolic beats, this formula became n + 3

REFERENCES

1 Steffens T G Intermittent ventricular paras tole du to entrance block failure Circulation 44 442, 197

2 Cohen H Langendorf R and Pick A Interm parasystole—mechanism of protection Cir 48 761 1973

3 Kinoshita S Wenckebach phenomenon of e block and intermittent ventricular parasys ole Ch 66 530 1974

4 Kinoshita S., and Tanabe Y Second degree entr block and intermittent ventricular parasystole Ch 67 236 1975

5 Schamroth L and Marriott H J L Interm ventricular parasystole with observations of its rela ship to extrasystolic bigeminy Am J Cardiol 7 1961

6 Schamroth L and Marriott H J L Concealed ventr ular extrasystoles Circulation 27 1043 1963

7 Lightfoot P R Concealed extrasystolic ventricul bigeminy with interpolation Chest 67 373 19 5

8 Salazar J and McKendrick C S Ventricular paras tole in acute myocardial infarction Br Heart J 32 3 1970

9 Baxter R H and McGuinness J B Comparison o ventricular parasystole with other dysrhythmias af acute myocardial infarction Am Heart J 88 4 1974

10 Hoffman B F The electrophysiology of the hea muscle and the genesis of arrhythmias in Dreifus L S and Likoff W editors Mechanism and therapy cardiac arrhythmias New York 1966 Grune & Strattor Inc p 33

11 Lightfoot P R Sinoatrial block with Wenckebac phenomenon and ventricular parasystole after myoca dial infarction Chest 65 664 1974

12 Scherf L and James T N The mechanisms of aber tion in late atrioventricular junctional beats Am Cardiol 29 529 1972

13 Lightfoot P R His bundle parasystole A form of A junctional parasystole Chest 66 695 1974

...ality of the mitral valve and a postexercise electrocardiogram showed no arrhythmias or ischemic changes

Comments

Surgical denervation of the esophagus although thought to interrupt the reflex pathway is not always completely successful in curing these patients Good symptomatic relief was obtained and not a complete cure by the use of a combination of propranolol and quinidine sulfate in this patient These disturbances of rhythm are thought to be due to the effect on the cardiac conducting system of a vagovagal reflex with the different impulses coming from the esophagus and the efferent discharges giving rise to the various arrhythmias These impulses originate either from the muscle receptors or from the sensory receptors situated in the mucosa

In the case reported by Kopald and associates[1] the surgical denervation of esophagus by bilateral vagotomy and distal esophagomyotomy did not completely cure the patient after a 4 year follow up In the case reported by Sapru and associates the patient was completely cured on a 2 year follow up In the case described by Alstrup and Pederson a cure is reported but the follow up is rather short It is clear from our case report and some of the previous case reports that surgery is not the whole answer to the problem and should be considered only if medical treatment is unsuccessful

In the patient who is the subject of this report a combination of surgical denervation and medical treatment has made the symptoms manageable and less troublesome A complete circular myotomy in theory denervates the esophagus effectively up to the submucosal autonomic plexus and if vagus was the sole conducting pathway should effectively interrupt this circuit The failure of a circular myotomy completely to abolish this reflex in this patient would suggest an alternative pathway other than through the two major vagal trunks Denervation is safe only distal to the origin of the recurrent laryngeal nerves and hence the upper third of the esophagus is likely to remain intact with its nerve supply This segment may well be responsible for some of the afferent impulses

The major drawback of a circular myotomy is its interference with the onward passage of a peristaltic wave which results in dysphagia On barium swallow examination it appears that the



Fig 2 Barium swallow 3 years after myotomy showing ballooning of mucosa and retraction of ends as shown by the metal clips placed at operation at the cut ends of the longitudinal muscle of the esophagus

mechanism of dysphagia in this case is due to lack of support to esophageal mucosa and subsequent ballooning which results in a tortuous passage for the food to negotiate Effective onward passage of food and drink requires a wave of peristalsis to pass in a sequential fashion down the esophagus and for this to happen effectively both the circular and the longitudinal muscles have to work in unison If the continuity of the muscle layer is interrupted by a procedure such as a circumferential myotomy then dysphagia results A major part of this difficulty could be overcome with the help of gravity and slow but satisfactory swallowing can be achieved in the upright position It is interesting to note that Davidson[8] using circumferential esophageal myotomy in 26 patients with hiatal hernia and peptic stricture observed only a smooth bulge at the site of myotomy which was present in certain phases of

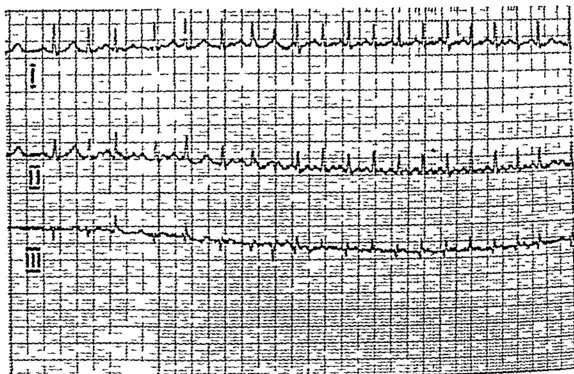


Fig 1A Standard leads of ECG showing atrial fibrillation on eating

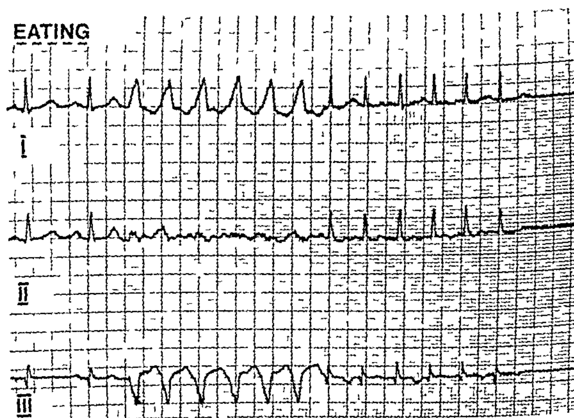


Fig 1B Standard leads of ECG showing ventricular tachycardia followed by supraventricular complexes on eating

symptoms on prophylactic oral propranolol and quinidine sulfate but this was effective for only a few months This treatment had been continued to the present day

A 3 year follow up showed that his symptoms were less troublesome although a minor degree of palpitations and dysphagia still occurred with food and drink regularly A barium swallow examination revealed considerable ballooning of esophageal mucosa at the site of the circular myotomy (Fig

2) Barium sulfate alone and barium with apple were swal- lowed and neither produced any arrhythmias on ECG moni- toring Clearance of apple from the ballooned area was slow but barium was cleared without any undue delay Esophageal manometry showed repetitive synchronous peristaltic waves of high pressures of up to 22 5 mm Hg Swallowing water and the tubes for manometric studies resulted in a short run of nodal tachycardia An echocardiogram showed no abnor-

linical pathologic conference

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ohn Collins Harvey M D
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linical summary

This 24 year old black man was in apparently ood health until approximately six months prior o admission when while stationed in Asia he egan to notice a gradual onset of fatigue and eight loss unassociated with any acute illness ever dysentery or other signs of infectious isease During his last four months in Asia he ost approximately twenty pounds despite a reasonably good appetite Approximately two nonths prior to admission he began to notice right upper quadrant abdominal tenderness which was accentuated by lying down and which occasionally worsened following meals Shortly after the onset of his abdominal tenderness he noticed dyspnea on exertion and orthopnea which rapidly progressed in severity with the appearance of bilateral pedal edema He was subsequently admitted to the hospital for evaluation of congestive heart failure

There was no family history of neuromuscular metabolic or premature cardiovascular disease He denied alcohol intake other than an occasional beer There was no known exposure to organic solvents or other chemical toxins

At physical examination the patient presented as a cachetic black man with marked muscle wasting of the upper extremities and a protuberant abdomen His vital signs were unremarkable with the exception of an irregular pulse Examination of the head ears eyes nose and throat were unremarkable The thyroid was not enlarged The neck veins were elevated at 8 cm His chest was clear to percussion and auscultation The point of maximal cardiac impulse was in the fifth intercostal space lateral to the anterior axillary line and had a dull prolonged thrust quality The first heart sound was normal but was followed by a Grade II/VI holosystolic murmur at the apex without radiation to the base or axilla The second heart sound was of normal intensity and split physiologically A third heart sound was present but no fourth heart sound was heard The liver measured 20 cm in the right pararectus line and 10 cm in the midline had a rounded edge and was slightly tender No abdominal masses were noted but there was shifting dullness and a fluid wave Edema with pitting on digital pressure was present over both shins and ankles There was marked muscle wasting of the shoulder girdle specifically the supraspinatus infraspinatus deltoid and pectoral muscles as well as the muscles of the anterior and posterior neck and face The quadriceps and gluteus muscles were similarly involved The distal extremity muscle groups appeared only slightly affected The patient s strength was decreased bilaterally but no muscle fasciculation or fibrillation was noted The remainder of the neurologic examination was within normal limits

The complete blood count (CBC) was normal on admission however atypical lymphocytes and anisocytosis with occasional target cells were noted during his hospital course Urinalysis was normal as were his serum electrolytes including calcium and phosphorus The cardiolipid microflocculation was nonreactive During hospitalization his serum glutamic oxaloacetic transaminase (SGOT) ranged from 70 to 334 units lactic dehydrogenase (LDH) from 800 to 1500 units creatine phosphokinase activity (CPK) from 372 to 750 units Lupus erythematosus (L E) preparations antinuclear antibodies DNA antibody

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swallowing and did not increase in size with the passage of time

Summary

A middle aged male patient with cardiac arrhythmias on swallowing due to incoordinate peristaltic activity of the esophagus is reported. Medical treatment with propranolol and quinidine sulfate made the symptoms manageable initially but recurrence of symptoms made surgical treatment desirable. Barium sulfate with apple produced the incoordinate peristalsis with resultant arrhythmias as soon as it arrived at the junction between the middle and lower third of the esophagus. This was followed by a normal peristaltic wave which cleared the esophagus and brought the cardiac rhythm back to normal again. Balloon distension of the esophagus located the afferent stimuli as arising from the lower third of the esophagus. A circular esophageal myotomy at the junction of the middle and the lower third although not completely abolishing the reflex has made the symptoms less severe. However this procedure has produced considerable ballooning of the mucosa at the myotomy site and has resulted in some difficulty in swallowing

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REFERENCES

1. Kopald H H Roth H P, Fleshler B and Pr... W H Vagovagal syncope Report of a case associated with diffuse esophageal spasm N Engl J M 271 1238 1964
2. Alstrup P and Pederson S A A case of syncope swallowing secondary to diffuse oesophageal spasm Acta Med Scand 193 365 1973
3. Correll H L, and Lindert M C F Vagovagal syncope Report of a case apparently induced by ... Am Heart J 37 446 1949
4. James A H Cardiac syncope after swallowing Lancet 1 751 1958
5. Levin B and Posner J B Swallow syncope Neurology 22 1086 1972
6. Tomlinson I W and Fox K M Carcinoma of the oesophagus with swallowing syncope Br Med J 2 315 1975
7. Sapru R P Griffiths P H Guz A and Eisele J Syncope on swallowing Br Heart J 33 61 1971
8. Davidson J S Circumferential oesophageal myotomy Br J Surg 59 938 1972

uld well reflect the disease of both his skeletal uscles and heart However on the basis of the mposite thyroid tests one would assume that thyrotoxicosis is present that the one elevated BI is probably a red herring and that the yopathies in this patient are not secondary to yperthyroidism

I would now like to have Dr Ross Fletcher omment on the electrocardiogram

DR ROSS FLETCHER First degree AV block is resent in both tracings The irregular rhythm on January 3 has essentially two P P and wo R R intervals one at 1 08 to 1 12 sec and the ther at 0 8 sec This suggests sinoatrial block erhaps in 4 3 or 3 2 Wenckebach periods with an nderlying sinus rate of 0 64 sec The P wave norphology does not vary making ectopic atrial ctivity an unlikely cause of the irregular hythm The P wave is broad with a prominent P erminal force in Lead V extending to Lead V_2 This left atrial abnormality points to left atrial nlargement with possible intraatrial conduction delay The P wave anterior force in Lead V_1 in ig 1B is twice as high as in Lead V on December 30 This increase coupled with the marked ncrease in QRS voltage from Leads V_1 to V_2 on January 3 points to right atrial enlargement A QRS V_1/QRS V_2 ratio of less than 30 per cent points to right atrial enlargement This ratio in Fig 1B is 3/13 or 23 per cent The frontal plane and Leads V and V_6 show low voltage in Figs 1A and 1B although this is more marked in Fig 1A The abnormal rightward QRS frontal plane axis of 115° (Fig 1B) points to right ventricular hypertrophy The axis was vertical at 90 in Fig 1A and this shift may indicate acute right heart strain such as that caused by pulmonary emboli Non specific ST T wave changes are present in inferior and lateral leads in Fig 1B which could be due in part to digitalis The combined SA and AV block suggest digitalis toxicity

DR W PROCTOR HARVEY It is important to remember that premature ventricular beats were present and these might well be forerunners of subsequent serious ventricular arrhythmias Also as Dr Fletcher mentioned the voltage was on the low side When low voltage is present on the electrocardiogram in a patient with an enlarged heart not only conditions such as a pericardial effusion emphysema and diffuse myocardial fibrosis should be considered but also amyloid cardiomyopathy However although this finding may be a clue to the presence of amyloid it is not specific The obvious disease of the skeletal muscles described in the patient under discussion make a diagnosis of amyloidosis unlikely

As far as this patient s cardiovascular system is concerned the history physical findings and clinical course are quite consistent with a cardio myopathy of the congestive type Although it was mentioned that his course was initially responsive to diuretics his improvement was only transient He was febrile with a temperature of 101° F Frequent causes of fever particularly in a patient who has a cardiomyopathy with chronic cardiac decompensation are multiple or recurrent pul monary emboli Pulmonary emboli may originate not only from clots present in either the right atrium or ventricle or both but also from the leg or pelvic veins Other causes of fever of course would be upper respiratory or urinary tract infec tions and these must be ruled out Since one of the most commonly overlooked complications in patients with chronic cardiac decompensation is that of pulmonary emboli anticoagulants may be indicated in these patients (unless of course there is some contraindication against the admin istration of anticoagulants) Sometimes the terminal event in these patients is a massive pulmonary embolus which seems likely in this patient It appears evident that we are dealing with a cardiomyopathy associated with a myopa thy involving the skeletal muscles I would now like to ask Dr John Collins Harvey if he would tell us some of the aspects of the myopathies and how they relate to this particular problem

DR JOHN COLLINS HARVEY The muscular dystrophies may be classified by the genetic pattern of transmission and by their appearance in relation to the age of the inflicted individual Duchenne muscular dystrophy and its Becker variety are inherited in a sex linked recessive pattern Duchenne muscular dystrophy makes its appearance in early childhood so that by the age of three the individual though having the appearance of large bulky muscles such as rather prominent gastrocnemius is quite weak falls considerably and may have difficulty in walking The disease is rapidly progressive so that many of the children are confined to a wheelchair by their ninth or tenth year and death often supervenes in the mid teens In this disease as in other primary myopathies there appears to be a leak in the muscle membrane so that enzymes involved

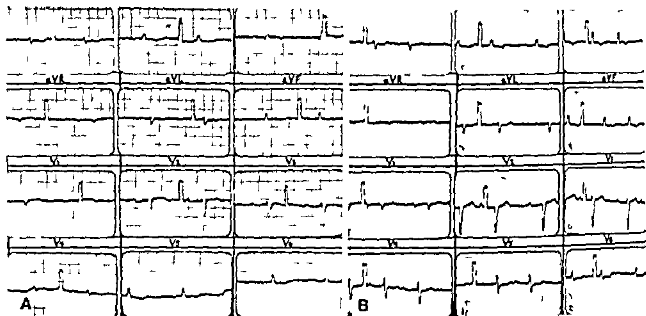


Fig 1 Sequential ECGs *A* December 30th *B* January 3rd

and latex fixation were all negative The serum complement titer was normal Complement fixation tests for mumps Coxsackie A and B virus were negative and the hemagglutination test for toxoplasmosis was negative The serum protein bound iodine (PBI) was greater than 25 0 micrograms/100 ml, T_4 index, 0 84 24 hour I^{131} uptake 18 per cent, thyroid gland not enlarged by I^{131} scan The electromyogram was abnormal with numerous myopathic action potentials in the proximal muscles Nerve conduction velocity was normal The electrocardiograms were abnormal with first degree AV block alternating with second degree AV block with episodic sinus arrest Wenckebach phenomenon, and multifocal premature ventricular contractions Cardiac x ray series was interpreted as generalized cardiomegaly with left ventricular and left atrial prominence without evidence of pulmonary congestion or pleural effusion A biopsy of the right deltoid muscle was obtained

Initially diuresis was effective with furosemide but the patient manifested only slight clinical improvement One week after his hospital admission, the patient became febrile (101° F) but an etiology was not elucidated His congestive heart failure progressively worsened and did not respond to digitalis, diuretics and prednisone He developed oliguria with azotemia and subsequently, cardiac arrest from which resuscitation was unsuccessful

DR W PROCTOR HARVEY The symptoms and signs, as described in this patient are quite characteristic of advanced cardiac decompensation and the protuberant abdomen might well be consistent with ascites associated with his cardiac decompensation Further evidence of his advanced state of cardiac decompensation is his greatly enlarged liver and the pitting edema of the lower extremities

It is pointed out that there was an irregular pulse which is indicative of an arrhythmia although this is not specific as to the exact cardiac arrhythmia present He also has a third heart sound which denotes a ventricular diastolic gallop (S_3 gallop) I would be very surprised that if carefully searched for he did not also have pulsus alternans and if he were having sinus beats, then an atrial gallop (S_4 gallop) might also be heard It is well appreciated that in order to detect these low frequency filling sounds (atrial and ventricular diastolic gallops) the patient must be turned to the left lateral position. The palpating fingers generally the index and third finger locate the point of maximum impulse of the left ventricle and the bell of the stethoscope is placed lightly over this area barely making an air seal With this simple but important maneuver these filling sounds (gallops) are often quite easily appreciated As we all know, they must be searched for to be routinely detected

Of particular importance in this patient is the muscle wasting of the upper extremities and the abnormal electromyogram It is apparent that in addition to his heart failure a myopathy is also present and the elevation of the serum enzymes

ild well reflect the disease of both his skeletal and heart However on the basis of the opposite thyroid tests one would assume that thyrotoxicosis is present that the one elevated]I is probably a red herring and that the opathies in this patient are not secondary to perthyroidism

I would now like to have Dr Ross Fletcher mment on the electrocardiogram

DR. ROSS FLETCHER First degree AV block is esent in both tracings The irregular rhythm on January 3 has essentially two P P and two R R intervals one at 1 08 to 1 12 sec and the her at 0 8 sec This suggests sinoatrial block rhaps in 4 3 or 3 2 Wenckebach periods with an nderlying sinus rate of 0 64 sec The P wave orphology does not vary making ectopic atrial ctivity an unlikely cause of the irregular ythm The P wave is broad with a prominent P rminal force in Lead V extending to Lead V his left atrial abnormality points to left atrial nlargement with possible intraatrial conduction elay The P wave anterior force in Lead V_1 in ig 1B is twice as high as in Lead V_1 on December 0 This increase coupled with the marked ncrease in QRS voltage from Leads V_1 to V_2 on January 3 points to right atrial enlargement A QRS V_1/QRS V_2 ratio of less than 30 per cent points to right atrial enlargement This ratio in Fig 1B is 3/13 or 23 per cent The frontal plane and Leads V_5 and V_6 show low voltage in Figs 1A and 1B although this is more marked in Fig 1A The abnormal rightward QRS frontal plane axis of 115 (Fig 1B) points to right ventricular hypertrophy The axis was vertical at 90° in Fig 1A and this shift may indicate acute right heart strain such as that caused by pulmonary emboli Non specific ST T wave changes are present in inferior and lateral leads in Fig 1B which could be due in part to digitalis The combined SA and AV block suggest digitalis toxicity

DR W PROCTOR HARVEY It is important to remember that premature ventricular beats were present and these might well be forerunners of subsequent serious ventricular arrhythmias Also as Dr Fletcher mentioned the voltage was on the low side When low voltage is present on the electrocardiogram in a patient with an enlarged heart not only conditions such as a pericardial effusion emphysema and diffuse myocardial fibrosis should be considered but also amyloid cardiomyopathy However although this finding may be a clue to the presence of amyloid it is not specific The obvious disease of the skeletal muscles described in the patient under discussion make a diagnosis of amyloidosis unlikely

As far as this patient s cardiovascular system is concerned the history physical findings and clinical course are quite consistent with a cardio myopathy of the congestive type Although it was mentioned that his course was initially responsive to diuretics his improvement was only transient He was febrile with a temperature of 101° F Frequent causes of fever particularly in a patient who has a cardiomyopathy with chronic cardiac decompensation are multiple or recurrent pul monary emboli. Pulmonary emboli may originate not only from clots present in either the right atrium or ventricle or both but also from the leg or pelvic veins Other causes of fever of course would be upper respiratory or urinary tract infec tions and these must be ruled out Since one of the most commonly overlooked complications in patients with chronic cardiac decompensation is that of pulmonary emboli anticoagulants may be indicated in these patients (unless of course there is some contraindication against the admin istration of anticoagulants) Sometimes the terminal event in these patients is a massive pulmonary embolus which seems likely in this patient It appears evident that we are dealing with a cardiomyopathy associated with a myopa thy involving the skeletal muscles I would now like to ask Dr John Collins Harvey if he would tell us some of the aspects of the myopathies and how they relate to this particular problem

DR JOHN COLLINS HARVEY The muscular dystrophies may be classified by the genetic pattern of transmission and by their appearance in relation to the age of the inflicted individual Duchenne muscular dystrophy and its Becker variety are inherited in a sex linked recessive pattern Duchenne muscular dystrophy makes its appearance in early childhood so that by the age of three the individual though having the appearance of large bulky muscles such as rather prominent gastrocnemius is quite weak falls considerably and may have difficulty in walking The disease is rapidly progressive so that many of the children are confined to a wheelchair by their ninth or tenth year and death often supervenes in the mid teens In this disease as in other primary myopathies there appears to be a leak in the muscle membrane so that enzymes involved

in the various metabolic processes such as creatine phosphokinase and aldolase, leak out into the serum and can be measured In Duchenne muscular dystrophy both of these enzymes are often elevated in the serum The myocardium is also involved in this disease process Such individuals have a characteristic electrocardiographic pattern with prominent R and Q waves in Lead I Very often these children die of myocardial failure

There is also a very mild form of this type of muscular dystrophy described some 15 years ago by a German pathologist, Becker This form of the disease appears to be identical in its expression to Duchenne muscular dystrophy but it may make its appearance somewhat later in life usually in the mid teens or early 20 s and follows a much milder course Patients with the Becker variety of muscular dystrophy may be able to ambulate for many years are only confined to a wheelchair in their late 30 s or early 40 s and live an extraordinarily long time The original description by Becker of these cases emphasized that there was no involvement of the myocardium The series of cases reported since that time however, have clearly shown that the myocardium is as involved in the Becker variety as it is in the Duchenne type of muscular dystrophy and death may occur in these patients as a result of cardiac arrhythmias or cardiac failure

Limb-girdle muscular dystrophy is transmitted in what appears to be an autosomal recessive pattern The muscle degeneration appears in the late teens or early 20 s but it may appear even later, in the early to mid 30 s Involvement of the skeletal muscle seems to be confined to shoulder girdle muscles and pelvic girdle muscles Facial muscles are spared and the disease progresses at a slow pace Individuals with this process may be able to ambulate well into their 40 s or 50 s before they are confined to a wheelchair It has been thought that cardiac muscle involvement does not exist in this form of muscular dystrophy but that is incorrect Several individuals in my own series and in other reported cases have died suddenly presumably from cardiac arrhythmias or in cardiac failure At autopsy the myocardium is as extensively involved as the skeletal muscles of the limbs

There are several forms of muscular dystrophy that are transmitted in the autosomal dominant pattern The first of these is facioscapulohumeral muscular dystrophy The muscle wasting involves the muscles of the face, the upper arm and scapula, hence its name There is usually wasting of the temporalis muscles involvement of the orbicularis occuli and occasionally of the masseter muscles Thus the patient is quite devoid of facial expression These individuals have winged scapulae and wasting of the biceps triceps and deltoid muscles The distal musculature however, is normal, and the pelvic girdle muscles are only rarely involved This disease usually manifests itself in the early or mid 20 s is very slowly progressive, and compatible with a long life Cardiomyopathy is rare in these individuals but does occur

Another form of autosomal dominant primary myopathy is myotonic muscular dystrophy This dystrophy is characterized by a prolongation of muscle contraction Myotonia may be seen in many skeletal muscles but is best exhibited in the tongue and in the muscles of the thenar eminence While its manifestations become clear in the late teens or early 20 s when one takes a history of such a patient one finds that the individual has always been clumsy, and has found it difficult to let go of things from early life onward This is the only muscular dystrophy in which distal muscles are involved The individuals are usually not bothered by the process until muscle wasting and weakness occur The course of illness is very slowly progressive although in some individuals ambulation may be difficult so that the individual is confined to a wheelchair in the mid or late 30 s The skeletal muscles of respiration are also afflicted and many individuals die of respiratory failure In myotonic muscular dystrophy the myocardium is involved and death may supervene as a result of cardiac arrhythmias or cardiac failure

In many of the acquired myopathies which are expressions of generalized disease processes the heart also is involved I believe that this correlation is probably more appreciated by the physician who studies muscle disease primarily rather than by the cardiologist For instance cardiac involvement is not uncommon in sarcoidosis polymyositis dermatomyositis rickettsialpox diphtheria or other infections

In this patient it is difficult to characterize his muscle disease precisely and I would like to see the skeletal muscle biopsy

Dr Hugh A McAllister The muscle biopsy

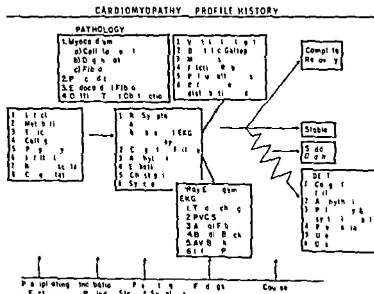


Fig 2 Cardiomyopathy Profile history (Reprodu ed from Segal J P., Harvey W P and Stapleton J F Clinical features and natural history of cardiomyopathy *in* Fowler N O ed Myocardial diseases New York, 1973 by permission Grune & Stratton Inc)

was obtained from the right deltoid muscle By light microscopy degenerating muscle fibers with eosinophilic and vacuolated cytoplasm were adja cent to normal appearing muscle fibers There was a striking absence of inflammatory cells and the arterioles and venules appeared normal Histochemical stains for muscle enzymes were non diagnostic but were interpreted as consistent with polymyositis

Dr John J Fenoglio Ultrastructurally the scattered degenerated muscle cells had frag mented sarcomeres vacuolated mitochrondria and areas of abnormal Z-band like material In the remaining muscle cells only focal widening of Z lines wa noted Nerve endings and vessels were unremarkable

Dr McAllister The microscopic ultras tructural and enzymatic findings are all nonspe cific and leave the pathologist with the same speculation as the clinician The paucity of inflammatory cells in this patient s muscular lesions makes the diagnosis of polymyositis diffi cult to consider strongly unless one also considers the variability of the pathology described in this group of patients and considers the possibility that the cellular inflammatory component may have been altered by the time course of the disease and by therapy especially with corticosteroids

Table I Etiology of cardiomyopathy

I Idiopathic (unknown)
II Specific etiology (known)
- A. Infectious (*viral* bacterial, mycotic parasitic protozoal rickettsial)
- B Connective tissue diseases
- C Metabolic (hyperthyroid hypothroid pheochromocytoma nutritional electrolyte imbalance)
- D Toxic (emetine carbon tetrachloride bacterial toxins, *cobalt*)
- E Alcoholic cardiomyopathy
- F Infiltrative (malignancy sarcoid hemachromatosis, amyloidosis, glycogen storage disease Fabry s disease gout oxalosis)
- G Neuromuscular disorders
- H Hypertrophic muscular outflow tract obstruction (obstructive cardiomyopathy)
- I Pregnancy—peripartum/postpartum
- J Congenital or familial myocardial disease
- K. Miscellaneous Endocardial fibroelastosis
  Endomyocardial fibrosis
  Hypersensitivity

Other possible etiologies for this patient s disease such as endocrine disorders (hypothyroid ism hyperthyroidism pheochromocytoma) nu tritional disorders (vitamin deficiency kwashior kor) noxious agents (heat stroke malignant hyperthermia chemicals and other toxins such as viper venom alcohol) and other neuromus cular disorders (muscular dystrophies myotonic

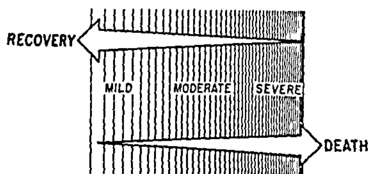


Fig 3 Cardiomyopathy A Spectrum (Reproduced from Segal J P Harvey W P and Stapleton J F Clinical features and natural history of cardiomyopathy in Fowler N O ed Myocardial diseases New York 1973 by permission Grune & Stratton Inc)

dystrophy, Friedreich's ataxia Refsum s syndrome myasthenia gravis periodic paralysis) seem unlikely both clinically and pathologically Systemic lupus erythematosus as well as other collagen vascular diseases may involve the skeletal as well as cardiac muscle but this possibility also seems similarly excluded

Dr Fenoglio A variant of facioscapulohumeral dystrophy must also be considered because of the distribution of muscle wasting in this patient The inheritance is usually dominant in this form of dystrophy therefore the absence of neuromuscular disorders in the family history is against this diagnosis Also facioscapulohumeral dystrophy usually begins in the second or third decade and is slowly progressive over a period of many years This patient s rapid and relentless course from good health to death over a period of seven months mitigates against this diagnosis Additionally although both cardiac and smooth muscle disease have been reported in facioscapulohumeral dystrophy cardiac involvement is rare and usually mild

It is known that the facioscapulohumeral distribution of muscle weakness is seen in a mixed bag of conditions including polymyositis The true dystrophy can usually be histologically differentiated from polymyositis by the hypertrophy of skeletal muscle fibers which is seldom seen in polymyositis and indeed this does not appear to have been a prominent feature in our patient Against the diagnosis of polymyositis, however, is the striking absence of inflammatory cells

Dr W Proctor Harvey It is evident that the patient presently under discussion fits in the neuromuscular group where the myocardium is involved as well as the skeletal muscles I would like to briefly review some of the pertinent features of cardiomyopathies in general before we review the autopsy findings in the patient under discussion

We prefer a broad classification of cardiomyopathy dividing those who have it into two groups (1) unknown etiology (idiopathic) and (2) known etiology (specific) As summarized in Table I and Fig 2 various infections are associated with cardiomyopathies, as well as diseases of connective tissue metabolic diseases toxins alcohol infiltrative diseases and neuromuscular disorders At times one sees patients where there is an obvious familial incidence In fact, just several days ago I examined a 21 year old man with a large heart who had Wolff Parkinson White syndrome His brother's electrocardiogram also showed WPW, but apparently without cardiomegaly It is very likely that this represents a familial type of cardiomyopathy

Cardiomyopathies occur at any age from infancy to old age, and the incidence in males and females is about equally divided Arrhythmias are of prime importance in these patients and any type of arrhythmia may occur including various conduction defects first, second and third degree heart block and right or left bundle branch block Left bundle branch block outnumbers right bundle branch block by approximately 2 5 to 1 The patient with cardiomyopathy may present with dizziness or syncope due to ventricular tachycardia or Stokes Adams syndrome as the first symptom At times multiple ventricular beats—sometimes multifocal in origin—are present and medical control may be difficult Patients having ventricular arrhythmias of this type are more prone to sudden death Chest pain both pleuritic and ischemic is not uncommon

Since congestive failure is so common gallop rhythm of the ventricular (or third sound) type is an expected finding Atrial gallops may be present even though congestive heart failure may not be a feature Gallop rhythms atrial or ventricular or both are hallmarks of cardiomyopathy of the congestive type Both gallops are frequently heard At times if the two gallop sounds occur simultaneously (exactly together) a loud sound may be produced which can be louder than either

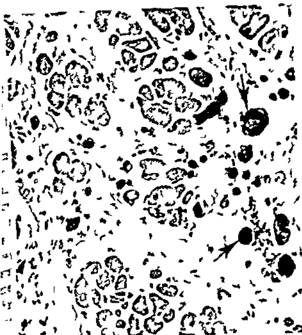


Fig 4 Focus of myocardial replacement by fibrous tissue The remaining myofibers are widely separated and scattered myofibers are degenerating (*arrow*) There is a striking absence of inflammatory cells (Hematoxylin and eosin ×165)



Fig 5 Degeneration of skeletal muscle fibers from the deltoid muscle Morphologically normal muscle fibers are indicated by arrows The muscle fibers are replaced by fibrous tissue and inflammatory cells are inconspicuous. (Hematoxylin and eosin original magnification ×140)

the first or second heart sound However this is uncommon and more frequently the two gallops occur in close proximity and may simulate a diastolic rumble In fact in years past we had several patients referred for mitral commissurotomy because of the presumed presence of a diastolic rumble plus other features that simulated rheumatic mitral stenosis

It is worthy of emphasis that cardiomyopathy is a spectrum (Fig 3) Some patients may have complete recovery On the other hand others progress to the severe end of the spectrum or death Sudden death is not uncommon in this group Patients can progress from a mild degree of the spectrum of cardiomyopathy to a more severe part or they may regress from a more severe to a less severe position As examples I recall two patients One lady is currently being followed in our cardiomyopathy clinic and was first seen following her last pregnancy Shortly after delivery she had symptoms and signs of cardiac decompensation Her electrocardiogram showed left bundle branch block Atrial and ventricular gallops and an apical systolic murmur were noted She has now been followed for 16 years She still has heart disease and remains in the chronic moderately severe spectrum of cardiomyopathy but is still able to work and carry on The other patient is a 23 year old woman who had a huge heart with multifocal ventricular premature contractions She was not improved by any medical treatment Approximately six years after the apparent onset of her problem (possibly related to a viral upper respiratory infection) she died suddenly (Viruses appear to be increasingly important as possible etiologic agents) Of great importance in patients with cardiomyopathy is early suspicion early diagnosis and early treatment I believe this is now occurring and as a result many patients can remain in or regress to the mild part of the spectrum and in some patients recovery is possible

In the patient being discussed today we are obviously dealing with the problem of cardiomyopathy The extra dimension is that we are also dealing with a skeletal myopathy The association of cardiomyopathy with skeletal myopathy is not common although we know from a group followed for a number of years in the muscular dystrophy clinic at our hospital that the heart as well as the skeletal muscles can be concomitantly involved When heart disease is present it may be significant and frequently is the cause of death It has become evident that we should be actively searching for the combination of diseases of the heart and skeletal muscles If we do we believe the association will be more common than real



Fig 6 The smooth muscle in this section of sigmoid colon is similarly affected by the apparent melting away Large areas of smooth muscle are replaced by fibrous tissue in the absence of inflammatory cells The arrows indicate relatively normal areas of smooth muscle (Hematoxylin and eosin ×210)

Table II Neuromuscular disease associated with cardiomyopathy

Duchenne muscular dystrophy
Beckers muscular dystrophy
Facioscapulohumeral dystrophy (Landouzy Dejerine)
Limb girdle dystrophy (Erb)
Distal forearm dystrophy (Gowers)
Ocular dystrophy
Myotonic dystrophy (Dystrophia myotonica)
Friedreich s ataxia
Refsum s syndrome
Peroneal muscular atrophy (Charcot Marie Tooth)
Myasthenia gravis
Myoclonic epilepsy (Lafora s Disease)

ized as exemplified by the patient being discussed

Dr McAllister At autopsy marked skeletal muscle wasting especially involving the shoulder girdle, cervical, facial, and pelvic muscle groups was present The heart weighed 454 G with marked dilatation of all the cardiac chambers especially the right ventricle The right ventricle was 3 mm thick and the left ventricle was 16 mm thick There were no grossly evident myocardial, endocardial or valvular lesions A mild fibrinous pericarditis without effusion was present The coronary arteries contained a few sc[illegible] atheromatous plaques, but all were pliable a[illegible] widely patent

There was massive pulmonary edema and are[illegible] of infarction were present in the lower lobes of both right and left lungs The arteries to both lungs contained multiple pulmonary thromboemboli There was phlebothrombosis of the left femoral vein

In sections of both atria and both ventric[illegible] there were large areas of muscle loss and fib[illegible] replacement (Fig 4) In some areas the fibr[illegible] tissue was loose and reticulated with a moderate acid mucopolysaccharide component The in[illegible] flammatory cell response was entirely mono[illegible] clear and was remarkably minimal Scattered Anitschkow cells were present in these lesions but no Aschoff bodies were noted There were focal, scattered nonspecific changes in the intra myocardial coronary arterioles consisting of smooth muscle loss and delicate intimal a[illegible] adventitial fibrosis but no exudative arterit[illegible] or fibrinoid necrosis was present Some sections of right atrial wall contained adherent partia[illegible] organized thrombi No parasites bacteria my[illegible] bacteria or fungi were detected utilizing spe[illegible] stains

The temporalis, supraspinatus gastrocnem[illegible] sartorius, pectoralis, and psoas muscles contained large areas of muscle loss with both degenerat[illegible] and regenerating muscle fibers and fibro[illegible] replacement similar to the myocardial lesio[illegible] (Fig 5) Both granular and vesicular degenerati[illegible] was present, and markedly involved muscle fibers were frequently adjacent to normal appear[illegible] fibers The small arterioles contained focal scat tered nonspecific changes consisting of smooth muscle loss and delicate intimal and adventi[illegible] fibrosis This latter observation was generally true of arteries and arterioles in other organs and the aorta also contained significant loss of smooth muscle with acid mucopolysaccharide replacement As in the heart no organisms were detected utilizing special stains

Sections of esophagus stomach small bowel appendix and urinary bladder contained large focal areas of smooth muscle loss with fibrous replacement (Fig 6) As in the sections of heart and skeletal muscle the cellular inflammatory response was sparse and entirely mononuclear

The thyroid gland and brain and spinal cord

were grossly and microscopically normal as was the thymus

The basic cause of death in this patient was a myopathy possibly a variant of polymyositis involving skeletal muscle cardiac muscle and smooth muscle The immediate cause of death was pulmonary thromboemboli with pulmonary infarction and massive pulmonary edema

The variability in the clinical and pathological manifestations of polymyositis coupled with ignorance concerning its etiology has made its classification difficult Twenty five per cent of patients with polymyositis have no cellular inflammatory response in the biopsy sections of affected muscle so that inflammation is not a sine qua non of the diagnosis The occurrence of myocardial involvement by this disease process that so closely resembles the patient's skeletal and smooth muscle involvement may be just another facet of this multifaceted syndrome

Although it is now generally recognized by clinicians and pathologists that cardiac involvement is part of the spectrum of the so called collagen vascular disease the association of the neuromuscular diseases with cardiomyopathy is not widely appreciated As is evident however from the discussions of Drs John Collins Harvey and W Proctor Harvey cardiac involvement is found in each of the neuromuscular diseases which for the sake of brevity are listed in Table II The extent and frequency of cardiac involvement in each of these diseases is not known primarily because we have not directed attention to this association and therefore we believe the coexistence of myopathy and cardiomyopathy has been largely overlooked by both clinicians and pathologists

REFERENCES

1. Hill D L and Barrows H S Identical skeletal and cardiac muscle involvement in a case of fatal polymyositis, Arch. Neurol 19 545 1968
2. Hudson R E B Cardiovascular pathology Baltimore 1965 The Williams & Wilkins Company vol 1 p 734
3. Lynch P G Cardiac involvement in chronic polymyositis Br Heart J 33 416 1971
4. Perloff J K DeLeon A C Jr., and O'Doherty D The cardiomyopathy of progressive muscular dystrophy Circulation 33 625 1966
5. Segal J P., Harvey W P., and Stapleton J F Clinical features and natural history of cardiomyopathy *in* N O Fowler ed Myocardial diseases New York 19 3 Grune & Stratton Inc p 37
6. Stapleton J F Segal, J P., and Harvey W P Clinical pathways of cardiomyopathy Circ Res 34 and 35 (Suppl. II) 168 19 4
7. Dubowitz, V., and Brooke H Muscle biopsy A modern approach, London 19 3 W B Saunders Company Ltd

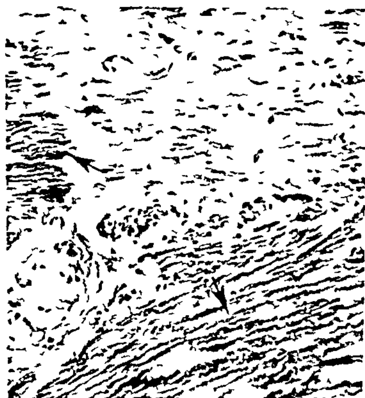


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Atrioventricular block Atrioventricular block of all degrees can be produced by cardiac glycosides and was reported as early as 1912 It also can be produced by increasing vagal tone through carotid sinus pressure by direct stimulation of the exposed vagus nerve and by stimuli originating in visceral afferents or medullary nuclei[1] As early as 1915 digitalis induced atrioventricular conduction defects ameliorated by atropine had been reported and subsequently numerous investigators have described digitalis induced atrioventricular block of various degrees reversed by atropine[1] [1] and laboratory studies as early as 1917 have shown that vagal section also is effective in reducing digitalis induced atrioventricular block almost to the point of elimination Particularly pertinent to the concepts being considered in the present paper is the fact that the degree of digitalis induced impairment of atrioventricular conduction can be influenced by variations in inducible vagal tone and therefore can be separated from inotropic effect This fact suggests that the configuration of the cardiac glycoside molecule may include an atropine reactive site and a separate structural moiety responsible for positive inotropicity which is uninfluenced by interreaction with atropine

Anorexia nausea and emesis It is recognized that vagal stimuli as well as vagomimetic drugs can produce nausea and emesis and that anorexia may represent a milder symptomatic manifestation of vagal effect than does nausea In animals severing neural connections between the heart and medulla prevents vomiting due to cardiac glycosides In man atropine ameliorates drug induced anorexia *nausea and vomiting including* that due to cardiac glycosides Probably when due to cardiac glycosides this triad of symptoms represents vagomimetic action It is known that the symptoms appear with parenteral administration as well as oral so that direct gastric irritative effect cannot be the explanation

Sympathomimetic effects of cardiac glycosides

Sympathomimetic drugs are divided into two pharmacologic types the catecholamines consisting of sympathomimetic amines with OH substitution in the aromatic O dihydroxybenzene ring (catechol) and the non catecholamines sympathomimetic drugs lacking the catechol nucleus Epinephrine and to a lesser extent norepinephrine are used commonly as prototypes of the catecholamines and mimic closely several effects of cardiac glycosides cited below [1] Such effects therefore may be referred to as sympathomimetic

Positive inotropic effect Cardiac glycosides are known to diminish end diastolic fiber length [4] decrease heart size [1] abbreviate duration of mechanical and of electromechanical systole [29, 3] increase stroke volume [31] enhance cardiac contractility *as demonstrated by strain gauge* increase mean systolic ejection rate [33] increase ventricular dP/dT [3] increase velocity of ventricular shortening [3] and increase velocity of myocardial depolarization [35] While the latter effect cannot in the restrictive sense be termed a positive inotropic effect it is a demonstrated companion of positive inotropicity The other effects itemized are demonstrable variants of positive inotropicity and since each can be produced either by cardiac glycosides or by epinephrine and or norepinephrine they may be appropriately referred to as examples of the sympathomimetic effects of cardiac glycosides

Myocardial electrical instability It is recognized that inappropriate sinus bradycardia may provide the setting for ectopic escape rhythms and sinus bradycardia is a parasympathomimetic effect of cardiac glycosides rather than a sympathomimetic effect Other than this contributory action of parasympathomimetic cardiac glycoside action to the production of ectopic rhythm it is probable that arrhythmias due to cardiac glycosides can be viewed as an extension of their sympathomimetic effect to the point of toxicity for sympathomimetic drugs of the catecholamine *type induce* identical ectopic rhythms at toxic dosage to those induced by cardiac glycosides Both cardiac glycosides and catecholamines enhance the latent capability of spontaneous depolarization of specialized and non specialized cardiac cells Interestingly phentolamine has been found to ameliorate myocardial electrical instability due either to epinephrine or to cardiac glycosides [37]

Autonomomimetic effects of cardiac glycosides

A drug possessing both sympathomimetic and parasympathomimetic effects may be referred to as an *autonomomimetic* drug It appears that such a designation may be applied with accuracy to the cardiac glycosides

The parasympathomimetic effects of cardiac

Fundamentals of clinical cardiology

Clinical implications of differences in pharmacodynamic action of polar and nonpolar cardiac glycosides

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Austin Texas

Recently differences in pharmacodynamic actions of cardiac glycosides have been described which may have clinical importance in man[1] Specifically it has been stated that ouabain, which is polar and digoxin which is moderately polar, appear to possess greater vagomimetic effect than the non polar glycoside digitoxin when each is given in dosage sufficient to produce the same amount of positive inotropic effect Atrioventricular block is cited as an example of vagomimetic effect[1]

Probably the therapeutic effects of cardiac glycosides can in fact be classified more broadly under one of two headings parasympathomimetic or sympathomimetic with the polar glycosides possessing relatively greater parasympathomimetic effect

The purpose of this paper is to present some of the evidence to support such a classification and to itemize the possible clinical implications of the apparent difference in pharmacodynamic action of the polar and the non polar cardiac glycosides

Parasympathomimetic effects of cardiac glycosides

Dale has been credited[4] with coining the term "parasympathomimetic in 1914 He noted that acetylcholine produced effects similar to those resulting from stimulation of parasympathetic nerves and termed this effect parasympathomimetic[5] The term 'cholinergic is applied [to] those autonomic nerve fibers which liberate acetylcholine or are activated by acetylcholine Atropine is known to inhibit the action of acetylcholine and therefore has some value in identifying cholinergic action of drugs With the e[fact] in mind there are several actions of cardiac glycosides which may be classified as parasympathomimetic, and as might be expected the site of action is not limited to the heart. However, several of the most important actions are upon the heart, and these can be produced by vagal stimulation as well as by cardiac glycosides and therefore may be referred to as vagomimetic

Sinus bradycardia Digitalis induced sinus bradycardia which can be abolished by atropine was reported as early as 1900[6] and most investigators since then have found that either cardiac denervation or atropine will prevent or abolish sinus bradycardia due to cardiac glycosides though some state that the reversal of bradycardia is not always complete[9 11] Sub total reversal of bradycardia by atropine might occur if a component of slowing secondary to increase in stroke volume were present yet increase in stroke volume cannot acount for all bradycardia because it has been shown that bradycardia due to cardiac glycosides may appear prior to increase in stroke volume[1]

Sinus arrest Sino atrial arrest may be produced by vagal stimulation as from carotid sinus pressure[13] and more than half a century ago was described as a toxic effect of digitalis[14] When produced by cardiac glycosides it can be abolished by atropine[15] and for this reason may be referred to as a toxic effect of the vagomimetic or parasympathomimetic action of cardiac glycosides

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Atrioventricular block Atrioventricular block all degrees can be produced by cardiac glyco les and was reported as early as 1912 [8] It also n be produced by increasing vagal tone through arotid sinus pressure by direct stimulation of ie exposed vagus nerve and by stimuli originat g in visceral afferents or medullary nuclei As arly as 1915 [8] digitalis induced atrioventric lar conduction defects ameliorated by atropine ad been reported and subsequently numerous nvestigators have described digitalis induced trioventricular block of various degrees reversed y atropine[29] [?] and laboratory studies as early as 917 have shown that vagal section also is effec i e in reducing digitalis induced atrioventricular block almost to the point of elimination Partic ularly pertinent to the concepts being considered n the pre ent paper is the fact that the degree of digitalis induced impairment of atrioventricular conduction can be influenced by variations in inducible vagal tone and therefore can be sepa rated from inotropic effect This fact suggests that the configuration of the cardiac glycoside molecule may include an atropine reactive site and a separate structural moiety responsible for positive inotropicity which is uninfluenced by interreaction with atropine

Anorexia nausea and emesis It is recognized that vagal stimuli as well as vagomimetic drugs can produce nausea and emesis and that anorexia may represent a milder symptomatic manifesta tion of vagal effect than does nausea In animals severing neural connections between the heart and medulla prevents vomiting due to cardiac glycosides In man atropine ameliorates drug induced anorexia nausea and vomiting includ ing that due to cardiac glycosides Probably when due to cardiac glycosides this triad of symptoms represents vagomimetic action It is known that the symptoms appear with parenteral administra tion as well as oral so that direct gastric irritative effect cannot be the explanation

Sympathomimetic effects of cardiac glycosides

Sympathomimetic drugs are divided into two pharmacologic types the catecholamines con sisting of sympathomimetic amines with OH substitution in the aromatic O dihydroxybenzene ring (catechol) and the non catecholamines sympathomimetic drugs lacking the catechol nucleus Epinephrine and to a lesser extent norepinephrine are used commonly as prototypes of the catecholamines and mimic closely several effects of cardiac glycosides cited below [33] Such effects therefore may be referred to as sympa thomimetic

Positive inotropic effect Cardiac glycosides are known to diminish end diastolic fiber length decrease heart size [2] abbreviate duration of mechanical and of electromechanical systole [2] [?] increase stroke volume [33] enhance cardiac con tractility as demonstrated by strain gauge [?] increase mean systolic ejection rate [33] increase ventricular dP/dT [34] increase velocity of ventric ular shortening and increase velocity of myocardial depolarization [36] While the latter effect cannot in the restrictive sense be termed a positive inotropic effect it is a demonstrated companion of positive inotropicity The other effects itemized are demonstrable variants of positive inotropicity and since each can be produced either by cardiac glycosides or by epinephrine and or norepinephrine they may be appropriately referred to as examples of the sympathomimetic effects of cardiac glycosides

Myocardial electrical instability It is recog nized that inappropriate sinus bradycardia may provide the setting for ectopic escape rhythms and sinus bradycardia is a parasympathomimetic effect of cardiac glycosides rather than a sympa thomimetic effect Other than this contributory action of parasympathomimetic cardiac glycoside action to the production of ectopic rhythm it is probable that arrhythmias due to cardiac glyco sides can be viewed as an extension of their sympathomimetic effect to the point of toxicity for sympathomimetic drugs of the catecholamine type induce identical ectopic rhythms at toxic dosage to those induced by cardiac glycosides Both cardiac glycosides and catecholamines enhance the latent capability of spontaneous depolarization of specialized and non specialized cardiac cells Interestingly phentolamine has been found to ameliorate myocardial electrical instability due either to epinephrine or to cardiac glycosides [3]

Autonomomimetic effects of cardiac glycosides

A drug possessing both sympathomimetic and parasympathomimetic effects may be referred to as an autonomomimetic drug It appears that such a designation may be applied with accuracy to the cardiac glycosides

The parasympathomimetic effects of cardiac

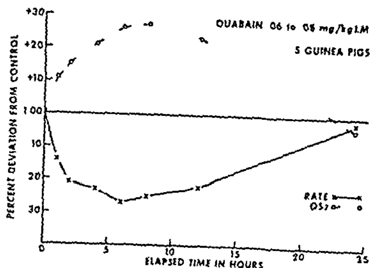


Fig 1 Ouabain Plot of percentage change in rate compared to percentage change in QS_2 Symmetrical graph (Graphs from Runge et al Pharmacodynamic distinctions within the cardiac glycoside family Biomed Eng Tech Reports University of Texas at Austin 731R 1 1973 Reproduced by permission)

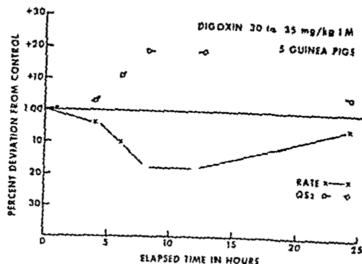


Fig 2 Digoxin Symmetrical graph similar to ouabain graph Compare *Fig 1* (Graphs from Runge et al Pharmacodynamic distinctions within the cardiac glycoside family Biomed Eng. Tech Reports University of Texas at Austin 731R 1 1973 Reproduced by permission)

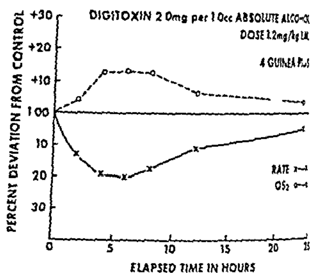


Fig 3 Digitoxin Abbreviation of electromechanical systole apparent and disproportional to reduction in rate produced assymmetrical graph $P < 0.05$ (Graphs from Runge et al Pharmacodynamic distinctions within the cardiac glycoside family Biomed Eng Tech Reports University of Texas at Austin 731R 1 1973 Reproduced by permission)

glycosides which are of principal interest to the clinician are atrioventricular blockade anorexia nausea and vomiting and to a lesser extent sinus bradycardia and sinus arrest each of which has been cited above and each of which also can be produced by acetylcholine In addition acetylcholine can depress amplitude of the P wave convert paroxysmal atrial tachycardia to normal sinus rhythm and can produce vertigo confusion and convulsions, as can also the cardiac glycosides The sympathomimetic effects of cardiac glycosides of principal interest to the clinician include positive inotropicity and increased myocardial electrical instability, both of which can be produced by epinephrine In addition s tachycardia, systemic arterial and venous constriction increased cardiac oxygen consumption increased rate of ventricular depolarization shortening of refractory period of ventricular muscle hyperventilation stupor convulsions elevation of serum potassium and myocardial necrosis can be produced by epinephrine but also by cardiac glycosides In fact a tabulation of the therapeutic and toxic effects of cardiac glycosides is strikingly similar to a tabulation of the combined effects of acetylcholine and epinephrine

Evidence for difference in degree of parasympathomimetic effect and sympathomimetic effect of polar and nonpolar cardiac glycosides

Almost a decade ago we began efforts to compare the pharmacodynamic effects of a spectrum of cardiac glycosides in intact unsedated animals for it seemed unreasonable to believe that the entire family of cardiac glycosides should have identical pharmacodynamic action and that it might therefore be possible to achieve greater precision in the clinical application of these agents Also there were suggestions by excellent clinicians that this might be the case Chavez[4] stated that he rarely if ever had a fatality due to the administration of the cardiac glycoside of his choice ouabain and McNamara[5] stated that it

is not unusual to see improvement in cardiac ilure in infants refractory to digoxin simply by witching to digitoxin Rational explanation for oth of these observations now appears at hand

Our early mammalian studies were in guinea gs Comparing the polar cardiac glycoside uabain to the relatively polar digoxin and to the latively non polar digitoxin it was found that hen dosage was sufficient to produce compa able reduction in sinus rate (20 per cent) that uration of electromechanical systole (QS_2) was ignificantly ($P < 0.05$) shorter with the non olar glycoside than with the polar ones suggest ig relatively greater positive inotropic (sympa homimetic) effect for the non polar cardiac lycoside (Figs 1 2 and 3) During the past two ears we have embarked upon a comparison of he effects in unsedated rabbits of intravenous ouabain digoxin and digitoxin recording the lectrocardiogram phonocardiogram and respi ation and also in each animal attempting to record the ballistocardiogram and the kinetocar liogram More than 100 studies have been performed representing almost as many animals and many have been studied for 72 hours recording the above data 13 times during this period The data thus far tabulated show greater vagomimetic effect with the polar glycosides than with the non polar as was the case in guinea pigs.

A review of the literature revealed that Krueger and Unna had stated without equivocation in 1942 that ouabain possessed an early vagal effect (sinus bradycardia) in cats which could be ablated with atropine and which was not possessed by digitoxin A clinical study reported by Aravanis and Luisada in 1958 showed greater reduction in heart rate (parasympathomimetic effect) with the polar cardiac glycoside digoxin but greater reduction in heart size (sympathomi metic effect) with the non polar glycoside digi toxin Other clinical studies were found suggest ing greater parasympathomimetic effects such as anorexia and nausea with polar glycosides A clinical study in volunteers by Weissler Snyder Schoenfeld and Cohen compared effects of intravenous ouabain 1 0 mg digoxin 1 6 mg and digitoxin 1 6 mg and the authors reported compa rable effect upon systolic time intervals How ever if one abstracts the rate data shown and plots it against ejection time index it can be seen that the polar cardiac glycosides depress sinus rate to a greater extent than the non polar glyco side when abbreviation of ejection time index is comparable With oral administration of 3 25 mg digoxin and 1 6 mg digitoxin comparable rate reduction was achieved with each drug but abbreviation of ejection time index was greater with digitoxin

In short data presently available from studies in animals and in man suggests that the parasym pathomimetic effects of cardiac glycosides such as sinus bradycardia atrioventricular block anorex ia nausea and vomiting are present to a higher degree in the polar glycosides while sympatho mimetic effects such as positive inotropicity and ectopic impulse formation are relatively stronger traits in the non polar cardiac glycosides Perhaps the low drug induced mortality rate Chavez[4] found with daily administration of ouabain was due to the dose limiting effect of anorexia or nausea so that serious ectopic rhythms did not occur Perhaps the success with digitoxin in cardiac failure unresponsive to digoxin described by McNamara was due to the fact that anorexia or other vagal effect limited dosage but was less prominent in relation to positive inotropicity in those infants switched to digitoxin

Discussion

Sequence of events in digitalization Following administration of cardiac glycosides in man it is probable that parasympathomimetic effect appears before sympathomimetic effect or at least is dominant early in digitalization One labora tory study in man supporting this concept is that of Masen and associates showing sinus brady cardia prior to increase in stroke volume Also supportive is the fact that the unmodified struc tural form of cardiac glycosides more closely resembles known parasympathomimetic agents than it does sympathomimetic agents[1] Further polar cardiac glycosides which are known to undergo relatively little biodegradation[4] mani fest relatively greater parasympathomimetic effect and non polar glycosides which are degraded in vivo manifest relatively greater sympathomimetic effect It is probable that the degradation converts the glycoside to a structure more suggestive of the catecholamines and its stepwise formation and final form have been postulated[1] Further it appears probable that the site of action of the polar glycosides is primarily extracellular but that the non polar

cardiac glycosides, which possess relatively greater sympathomimetic effect act not only at extracellular sites, but to a greater degree than do the polar glycosides at intracellular sites[37] The principal factor limiting the polar agents to the cell exterior probably is the clumping tendency supplied by the polar molecules one binding to the other, producing relatively large aggregates of molecules sometimes in clumps and sometimes in sheets, but in either case offering less exposed surface area for biodegradation than is afforded by the non polar non aggregated molecules of digitoxin

The concept of in vivo conversion of a molecule from a parasympathomimetic structure to a sympathomimetic structure probably has a parallel in acetylcholine itself which not only manifests parasympathomimetic effects but in high dosage may produce tachycardia palpitation and bounding pulse which sometimes are referred to as the nicotinic action of acetylcholine but which perhaps might instead be referred to as the sympathomimetic effect of acetylcholine and represent a partial conversion of the molecular aggregate to a sympathomimetic configuration a metamorphosis which actually would require little structural modification Another example of the presence of various degrees of parasympathomimetic and sympathomimetic effect within a single molecule is available in the family of the so called β adrenergic blocking agents dichloroisoproterenol pronethalol propranolol and sotalol each of which can be considered derivatives of the β receptor stimulant isoproterenol[4] and each of which may manifest in addition some degree of intrinsic β receptor stimulation that is, sympathomimetic effect The extent of the sympathomimetic potential of dichloroisoproterenol and pronethalol is great enough to practically preclude their clinical employment for β blockade and from our own observation can also be a problem with propranolol in some patients

In short, the concept of a dual role for cardiac glycosides, that is both a sympathomimetic and a parasympathomimetic moiety, with the former dominating in the non polar agents and the latter in the polar agents, probably is not a feature unique to the class Further it appears that the structural configuration responsible for parasympathomimetic effect is different from that responsible for sympathomimetic effect, as the former can be ablated either upon the molecule itself or at the site of action of the molecule on the cell b atropine

Toxicity of cardiac glycosides as related to polarity Since polar cardiac glycosides poss greater parasympathomimetic effect than no polar glycosides, the former should be particu larly useful in clinical settings benefited by vag tonicity, but should be considered less desirable than the non polar glycosides if there exists a degree of atrioventricular block Several clinical settings will be cited as examples in which o cardiac glycoside could be expected to be more toxic or more beneficial than another based up its polarity

Polar cardiac glycoside preferred Paroxysmal atrial tachycardia uncomplicated by other evi dence of cardiac disorder and not secondary to medication often can be converted to norm sinus rhythm by vagal stimuli and by vagom metic or parasympathomimetic med atio such as neostigmine[50, 51] edrophonium acety methylcholine[53] acetylcholine[54] procainamide and cardiac glycosides[56] When a cardiac gly side is used it is customary to use the moderate polar digoxin or one of its variants lanatosid or lanatoside D because of their early onset action However this proves to be a fortu choice since these agents possess greater vagom metic effect than digitoxin Ouabain should b excellent but is not satisfactory for maintena because of its parenteral requirement Whe ventricular ectopics or hypokalemia complicate paroxysmal tachycardia non polar glycoside such as digitoxin should be avoided because of their tendency to initiate or aggravate ectopi impulse formation When cardioversion is ant ipated polar glycosides should afford less oppo tunity for post conversion ectopic rhythms tha if the patient has received a non polar prepara tion provided the degree of parasympathom metic effect achieved has been comparable

Atrial flutter and atrial fibrillation are no consistently converted to normal sinus rhythm by cardiac glycosides but consistent reduction in the number of supraventricular impulses reaching the ventricles can be achieved with proper admi istration of cardiac glycosides When cardia failure due to valvular disease or myocardia disease is not a problem the polar glycoside should be used since the vagal effect impair atrioventricular conduction is the desired phar macodynamic action If cardiac failure i prese

ue in part to myocardial dysfunction and not solely to rapid ventricular rate the polar glycoside may not suffice and nausea or excessive trioventricular block may ensue prior to sufficient positive inotropic effect This may occur also in valvular heart disease as in mitral stenosis with a large pressure gradient across the mitral valve complicated by coexistent myocardial dysfunction and left ventricular failure Due perhaps to atrial volume overloading and associated facilitation of anomalous atrioventricular conduction pathways such patients sometimes appear to require greater ventricular ejection fraction than can be produced by a polar cardiac glycoside at less than toxic vagomimetic dose Presumably the non polar glycoside by increasing stroke volume alleviates volume overload of the atrium and removes the responsible pathogenic mechanism

Atrial ectopics normally can be expected to respond to vagomimetic therapy so should be more susceptible to polar than to non polar cardiac glycoside The exception to be anticipated is the patient with atrial volume overloading due to ventricular failure in which case positive inotropicity of large magnitude may be necessary in addition to the ectopic depressive vagomimetic quality of cardiac glycosides

Non polar cardiac glycoside preferred Atrioventricular block when due to cardiac glycosides is a parasympathomimetic effect If it occurs prior to achievement of the desired degree of positive inotropic effect in a patient receiving a polar cardiac glycoside switching to a non polar glycoside should be beneficial by allowing a greater degree of positive inotropicity for a given amount of vagomimetic effect Also in the patient with any degree of atrioventricular conduction impairment prior to digitalization a non polar glycoside ordinarily would be preferred for the same reason

Inappropriate sinus bradycardia due either to excessive intrinsic vagal factors non cardiac medication or malfunction of the sinoatrial node constitutes a relative indication for administration of a non polar rather than a polar cardiac glycoside when the purpose of glycoside administration is to alleviate cardiac decompensation In making this recommendation it is assumed that the ventricular rate is sufficiently slow to be less than optimal for the patient under consideration Similarly if excessive sinus bradycardia appears in a patient after beginning digitalization with a polar cardiac glycoside simply switching to a non polar glycoside can be expected to accelerate the ventricular rate without diminishing the degree of induced positive inotropic effect

Anorexia nausea or emesis prior to digitalization or occurring with a polar cardiac glycoside prior to achievement of optimal positive inotropicity constitutes an indication for switching to a non polar cardiac glycoside since this triad ordinarily represents excessive vagotonicity

Additional differences in polar and non polar cardiac glycosides

Several additional differences in action of polar and non polar cardiac glycosides can be itemized some of which probably are related to the fact that polar agents offer a smaller reactive surface area and some of which probably are related to the fact that the more highly substituted sterol components of the polar agents limit available binding sites Among these differences are the diminished tendency to protein binding of the polar glycosides their relatively poor absorption by mouth and their rapid onset but relatively brief duration of action[54] While all cardiac glycosides influence potassium mechanics and concentration this capability is greater probably with the non polar glycosides than with the polar and there are reasons to believe that positive inotropicity induced by cardiac glycosides ordinarily is associated with an increase *in ratio of* intracellular to extracellular potassium concentration despite the fact that cardiac glycosides have frequently been reported to cause myocardial potassium wasting

Effects of cardiac glycosides which are neither parasympathomimetic nor sympathomimetic in type

Earlier the comment was made that a complete tabulation of the effects of acetylcholine and epinephrine constituted a reasonable approximation of the effects of the cardiac glycosides The exceptions consist of several effects of cardiac glycosides which are linked to the cyclopentaperhydrophenanthrene moiety and include estrogenic effect upon vaginal epithelium of postmenopausal women[5] and gynecomastia in men Insulin like action reduction in plasma glycerol[43] and thrombocytopenia[4] probably represent *autonomomimetic* action as may also blurred

yellow, and white vision though perhaps the visual symptoms are migr unoid and linked to the sterol moiety

Summary

The principal effects of cardiac glycosides probably can be classified as parasympathomimetic or sympathomimetic. Data from animals and from man suggest that polar cardiac glycosides, such as ouabain and digoxin possess greater parasympathomimetic (vagal) cardiac effect for a given amount of sympathomimetic (positive inotropic) cardiac effect than do less polar cardiac glycosides, such as digitoxin. Polar glycosides therefore offer some advantage in uncomplicated paroxysmal atrial tachycardia and in uncomplicated atrial flutter and atrial fibrillation when the principal desired effect is reduction in the number of atrial impulses reaching the ventricles or conversion to normal sinus rhythm. Non polar glycosides offer an advantage when positive inotropicity is desired but when there is some degree of atrioventricular block or when inappropriate sinus bradycardia or anorexia nausea or vomiting are present. Ectopic impulse formation when due to cardiac glycosides is a toxic manifestation of excessive sympathomimetic effect but is aggravated by vagal induced sinus bradycardia so that both parasympathomimetic and sympathomimetic capability of cardiac glycosides must be considered when dealing with myocardial electrical instability

REFERENCES

1 Runge T M Stephens J C Holden P Havemann D F Kilgore W M Dale E M and Dalton R E Pharmacodynamic distinctions between ouabain digoxin and digitoxin Arch Int Pharmacodyn 214 31 1975

2 Runge T M Stephens J C Holden P Havemann D F Kilgore W M Dale E M and Dalton R E Pharmacodynamic distinctions within the cardiac glycoside family Biomed Eng Tech Reports University of Texas at Austin 731R 1 1973

3 Runge T M Cardiac glycosides categorization of effect as vagomimetic and inotropic Biomed Eng Tech Reports University of Texas at Austin 733TR 1 1973

4 Koelle G B Parasympathomimetic agents *in* The pharmacological basis of therapeutics 4th ed Goodman L S and Gilman A eds London Toronto New York 1970 Macmillan Co pp 466 477

5 Dale H H The action of certain esters and ethers of choline and their relation to muscarine J Pharmacol Exp Ther 6 147 1914

6 Gove P B (ed) Webster's Third New International Dictionary (unabr) p 397 1966

7 Innes I R and Nickerson M Drugs inhibiting the action of acetylcholine on structures innervated by postganglionic parasympathetic nerves (antimuscarinic or atropinic drugs) *in* The pharmacological basis of therapeutics 4th ed Goodman L S and Gilman A eds London Toronto New York 1970 Macmillan Co 524 548

8 Arnold J P and Wood H C Jr A comparative [illegible] of digitalis and its derivatives Am J Med Sci 120 1900

9 White P D and Sattler R R Effect of digitalis on the normal human electrocardiogram with especial reference to A V conduction J Exp Med 23 613 1916

10 Chai C Y Wang H H Hoffman B F and W[illegible] S C Mechanisms of bradycardia induced by d[illegible] substances Am J Physiol 212 26 1967

11 Ten Eick R E and Hoffman B F Chronotropic effect of cardiac glycosides in cats dogs and rabbits Circ Res 25 365 1969

12 Maseri A Bianchi R Giusti C Toni P and D[illegible] L Early effects of digitalis on central hemodynamics in normal subjects Am J Cardiol 15 16[illegible] 196[illegible]

13 Bellet S Sinus irregularities *in* Clinical disorders of the heart beat Bellet S ed Philadelphia 19[illegible] Lea & Febiger p 149

14 White P D Auricular standstill An unusual effect of digitalis on the heart with especial reference to the electrocardiogram Boston Med Surg J 175 [illegible] 1916

15 Navab A and Honey M Self poisoning with digoxin Successful treatment with atropine Br Med J 3 [illegible] 1967

16 Cushny A R Marris H and Silverberg M D The action of digitalis in therapeutics Heart 4 33 191[illegible]

17 Bellet S A V heart block *in* Clinical disorders of the heart beat Philadelphia 1971 Lea & Febiger p 3[illegible]

18 Cohn A E Clinical and electrocardiographic studies on the action of digitalis J A M A 65 1527 1915

19 Carleton R A Miller P H and Graettinger J [illegible] Effects of ouabain atropine and ouabain and atropine on A V nodal conduction in man Circ Res 20 [illegible] 1967

20 Miller P H Efficacy of atropine in the treatment of digitalis induced A V block Dis Chest 56 [illegible] 1969

21 Smith T W and Willerson J T Suicidal and accidental digoxin ingestion Circulation 44 [illegible]9 1971

22 Robinson G C and Wilson F N A quantitative study of the effect of digitalis on the heart of the cat J Pharmacol Exp Ther 10 491 1917 18

23 Ogden P C Selzer A and Cohn K E The relationship between the inotropic and dromotropic effects of digitalis Modulation of these effects by autonomic influences Am Heart J 77 628 1969

24 Hatcher R A and Weiss S The seat of the action of the digitalis bodies J Pharmacol Exp Ther 32 3 1927 28

25 Innes I R and Nickerson M Drugs acting at postganglionic adrenergic nerve endings and structures innervated by them (sympathomimetic drugs) *in* The pharmacological basis of therapeutics 4th ed Goodman L S and Gilman A eds London Toronto New York 1970 Macmillan Co pp 478-523

26 Bijlsma V G and Roessingh M J Die dynamik des saugetierherzens unter dem einfluss von [illegible]toffen der digitalisgruppe Arch Exp Path Pharm 94 23[illegible] 19[illegible]

27 Strong G F and Gordon G Studies on the rabbit's heart Effect of strophanthin on the size of the normal and of the abnormal heart Arch Intern Med 32 510 1923

28 Cohn A E and Stewart H J Relation between cardiac size and cardiac output per minute following

administration of digitalis Proc Soc Exp Biol Med 25 304 1928
3 Wiggers C J and Stimson B Studies on the cardiodynamic actions of drugs III The mechanism of cardiac stimulation by digitalis and g strophanthin J Pharmacol Exp Ther 30 251 1926 27
Cotten M DeV and Bay E Direct measurement of changes in cardiac contractile force Am J Physiol 187 122 1956
Harvey R M Ferrer M I Cathcart R T Richards D W Jr and Cournand A Some effects of digoxin upon the heart and circulation in man Am J Med 7 439 1949
Walton R P Leary J S and Jones H P Comparative increase in ventricular contractile force produced by several cardiac glycosides J Pharmacol Exp Ther 98 346 1950
33 Murphy G W Schreiner B F Bleakley P L and Yu P N Ventricular performance following digitalization in patients with and without heart failure Circulation 30 358 1964
34 Mason D T and Braunwald E Studies on digitalis IX Effects of ouabain on the non failing human heart J Clin Invest 42 1105 1963
35 Sonnenblick E H Williams J F Jr Glick G Mason D T and Braunwald E Studies on digitalis XV Effects of cardiac glycosides on myocardial force velocity relations in the nonfailing human heart Circulation 34 532 1966
36 Pruett J K and Woods E F The relationship of intracellular depolarization rates and contractility in the dog ventricle in situ Effects of positive and negative inotropic agents J Pharmacol Exp Ther 157 1 196
37 Ettinger S Gould L Carmichael J A and Tashjian R J Phentolamine Use in digitalis induced arrhythmias, AM HEART J 77 636 1969
38 Chavez I Comparative value of digitalis and of ouabain in the treatment of heart failure Arch Intern Med 72 168 1943
39 McNamara D G Personal communication Oct 29 19 1
40 Krueger E and Unna K Comparative studies on the toxic effects of digitoxin and ouabain in cats J Pharmacol. Exp Ther 76 282 1942
41 Aravanis C and Luisada A A Clinical comparison of six digitalis preparations by the parenteral route Am J Cardiol 1 06 1958
42 Wax D and Kirshner J Comparison of toxic manifestations produced by three cardiac glycosides digitoxin digoxin and acetyl digitoxin Fed Proc 15 497 1956
43 Shrager M W Digitalis intoxication Arch Intern Med. 100 881 1957
44 Weissler A M Snyder J R Schoenfeld C D and Cohen S Assay of digitalis glycosides in man Am J Cardiol 17 68 1966
45 Runge T M Theoretical structure activity relationships of cardiac glycosides Biomed Eng Tech Reports University of Texas at Austin 73TR 2 19 3
46 Ashley J J Brown B T Okita G T and Wright S E The metabolites of cardiac glycosides in human urine J Biol Chem 232 315 1958
47 Runge T M Cardiac glycosides Polarity as related to myocardial cation concentration and current of injury Electron Res. Center Tech. Reports University of Texas at Austin 177 1 1976
48 Nickerson M Drugs inhibiting adrenergic nerves and structures innervated by them in The pharmacological basis of therapeutics 4th ed Goodman L. S., and Gilman A eds London, Toronto New York 19 0 Macmillan Co pp 565-5 3
49 Bellet S Paroxysmal atrial tachycardia in Clinical disorders of the heart beat Philadelphia 1971 Lea & Febiger p 374
50 Battro A Segura G R and Lanari A El prostigmin en el tratamiento de las taquicardias paroxisticas supraventriculares Medicina Buenos Aires 1 383 1941
51 Waldman S and Pelner L Action of neostigmine in supraventricular tachycardias Am J Med 5 164 1948
52 Moss A J and Aledort L M Use of edrophonium (Tensilon) in the evaluation of supraventricular tachycardia Am J Cardiol. 17 58, 1966
53 Starr I Jr Acetyl β methylcholine IV Further studies of its action in paroxysmal tachycardia and in certain other disturbances of cardiac rhythm Am J Med. Sci 191 210 1936
54 Abbott K H Acetylcholine in paroxysmal tachycardia J A M A 113 1743 1939
55 Berry K Garlett E L, Bellet S and Gefter W I Use of pronestyl in treatment of ectopic rhythms. Am J Med 11 431 1951
56 Wilson F N and Wishart S W Effect of intravenous administration of digitalis in paroxysmal tachycardia of supraventricular origin AM HEART J 5 549 1930
57 Weisberger A S and Feil H Lanatoside C in treatment of persistent paroxysmal tachycardia, AM HEART J 34 8 1 194
58 Moe G K and Farah A E Digitalis and allied cardiac glycosides in The pharmacological basis of therapeutics 4th ed Goodman L S and Gilman A ed London Toronto New York 19 0 Macmillan Co., p 697
59 Hajdu S and Leonard E The cellular basis of cardiac glycoside action Pharmacol Rev 11 173 19 9
60 Navab A Koss L G and LaDue J S Estrogen like activity of digitalis J.A.M.A 194 142 1965
61 Singer E P Gynecomastia following digitalis administration J Med Soc N J 64 507 1967
62 Ho R J Jeanrenaud B., Posternak, T and Renold A E Primary antilipolytic effect through inhibition of adenyl cyclase Biochem Biophys Acta 144 74 1967
63 Triner L. Kypson J and Nahas G G Hypoglycemic effect of ouabain in dogs Proc Soc Exp Biol Med 127 1255 1968
64 Young R C Nachman, R L. and Horowitz H I Thrombocytopenia due to digitoxin Am. J Med 41 605 1966
65 Luisada A A Digitalis poisoning in a case of hyperthyroidism Dis Chest 54 66 1968

Ventricular unloading in the management of heart disease Role of vasodilators Part I

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Bronx N Y

For a long time vasodilators have been used for a variety of cardiovascular disorders especially angina pectoris It is only recently that their indications have been extended to include congestive heart failure, valvular regurgitation, and acute myocardial infarction

The rationale behind the use of such agents has evolved from an understanding of various factors that modify the function of the left ventricle as a pump and regulate myocardial oxygen consumption and delivery

The principal determinants of left ventricular pump function are preload afterload contractile state and left ventricular wall synergy [1] Normally there is a curvilinear relationship between left ventricular preload (left ventricular end diastolic volume) and its stroke work as expressed by the Frank Starling ventricular function curve Beyond a certain limit increases in preload may not increase stroke work, and in certain situations an actual decrease in stroke work may be observed suggesting the existence of a descending limb in the Frank Starling curve An increase in end diastolic volume is utilized by a failing left ventricle in order to maintain a near normal stroke volume in the early phases of left ventricular dysfunction

Ventricular afterload is regulated by the impedance which is offered to the ventricle during its ejection and is chiefly determined by arterial blood pressure which in turn depends upon the peripheral vascular resistance and cardiac output Ventricular fiber shortening and afterload vary inversely Therefore, an increase in afterload tends to decrease the stroke volume Congestive heart failure is usually characterized by a decrease in cardiac output with a compensatory increase in peripheral vascular resistance in order to maintain mean arterial pressure within the normal or near normal range In the presence of left ventricular dysfunction this increase in peripheral vascular resistance further impedes ventricular ejection

Contractile state is the inherent strength and speed of contraction of the cardiac muscle independent of preload and afterload

In ischemic heart disease segmental contraction abnormalities are frequently found. Such abnormal segments may contribute to decreased pump performance by being hypokinetic or akinetic, making little or no contribution to stroke volume Also a significant volume displacement may be dissipated in the expansion of a dyskinetic segment

Rationale for the use of vasodilators (Fig 1)

Congestive heart failure Major signs and symptoms of congestive heart failure are caused by elevation of pulmonary (and systemic) venous pressures and reduced cardiac output Symptomatic therapy is aimed at reducing the elevated pulmonary (and systemic) venous pressures and enhancing cardiac output Conventional modes of therapy have utilized preload reduction with diuretics (and low salt diet phlebotomy, rotating tourniquets and dialysis) for reducing pulmonary vascular congestion and positive inotropic agents like digitalis compounds (and catecholamines and paired pulse stimulation) to augment cardiac output Although these modalities are effective in managing most patients with congestive heart failure adverse clinical effects may be encountered Diuretics may produce serious acid-base and potentially life threatening electrolyte disturbances and have not been shown to increas

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Fig 1 Schematic diagram showing mechanism of action of vasodilator in congestive heart failure and valvular regurgitation MVO = myocardial oxygen consumption EDV = end diastolic volume EDP = end-diastolic pressure PWP = pulmonary wedge pressure VSD = ventricular septal defect SV = stroke volume ESV = end systolic volume CO = cardiac output

cardiac output In certain situations especially acute myocardial infarction a vigorous diuresis may produce a drop in cardiac output and serious hypotension In severe congestive heart failure even large doses of potent diuretics may become ineffective in augmenting urine flow

Digitalis glycosides can cause serious life threatening arrhythmias especially in the presence of hypokalemia and acute myocardial infarction Furthermore they are often ineffective in the management of severe refractory heart failure Digitalis has not been shown to consistently improve cardiac output during myocardial infarction[3] and may actually increase peripheral vascular resistance and afterload In view of oxygen wasting effects of increased afterload and the augmented inotropic state digitalis has the potential to increase myocardial oxygen demand However a decrease in end diastolic volume in a dilated ventricle and slowing of a rapid heart rate may decrease the myocardial oxygen demand tending to counterbalance its oxygen wasting effects.

Recently a decrease in impedance to left ventricular ejection by afterload reducing vasodilator agents has been utilized in the management of acute and chronic congestive heart failure and low cardiac output states It has been shown that in congestive heart failure of various etiologies potent vasodilators decrease peripheral vascular resistance and thereby afterload Reduced afterload enhances myocardial fiber shortening resulting in a decreased left ventricular end systolic volume associated with increased stroke volume Most vasodilators also have a variable degree of venodilator effect thereby causing venous pooling which reduces preload Decrease in end diastolic volume (preload) results in a decrease in left ventricular end diastolic pressure and pulmonary capillary wedge pressure thereby relieving signs and symptoms of pulmonary congestion Depending upon the relative magnitude of effects on preload and afterload the net result is usually an increased or unchanged stroke volume with a reduced pulmonary capillary wedge pressure implying an improved ventricular function or leftward shift to a more normal Frank Starling relationship Often there is little or only a modest decrease in mean arterial pressure even in relatively hypotensive patients because the improved cardiac output tends to counterbalance the effect of decreased peripheral resistance

Table I Commonly used vasodilators

Parenteral	*Non parenteral*
1 Sodium nitroprusside	1 Nitrates—Sublingual nitroglycerin and isosorbide dinitrate Chewable isosorbide dinitrate Oral isosorbide dinitrate Topical nitroglycerin
2 Phentolamine	2 Hydralazine
3 Trimethaphan	3 Phenoxybenzamine
4 Nitroglycerin	

Table II Conversion of sodium nitroprusside

Sodium Nitroprusside	SH groups of tissues and RBC →	Cyanogen	Hepatic Rhodanase (Transulfurase) → ← RBC thiocyanate oxidase	Thiocyanate Excreted by kidney

The major determinants of myocardial oxygen demand are wall tension (preload × afterload)/wall thickness heart rate and contractile state[5] The improved pump performance by vasodilators is produced with a uniform decrease in wall tension often with little if any change in heart rate Except for phentolamine no direct positive inotropic effect has been demonstrated with the commonly used vasodilators Although a reflex increase in contractility due to increased sympathoadrenal activity is possible it seems unlikely in most instances where no concomitant changes in heart rate are observed Thus reduced oxygen demand may be coupled with an increase in transmural coronary flow gradient (aortic diastolic pressure minus left ventricular diastolic pressure) and this may generally counterbalance the possible deleterious effects of a reduction in coronary perfusion pressure (aortic diastolic pressure)

Valvular regurgitation The effect of changes in afterload on the severity of valvular regurgitation is well known Decreased impedance to left ventricular ejection induced by vasodilators can improve forward flow with a reduced regurgitant fraction It is probable that improved left ventricular pump function and decrease in dynamic regurgitant orifice size (in case of mitral regurgitant) may contribute to improved hemodynamics Common vasodilating drugs are shown in Table I

Sodium nitroprusside Sodium nitroprusside is a water soluble crystalline substance which forms a light brown photosensitive solution Exposure to light converts the ferric iron to the ferrous form and this is associated with loss of pharmacological activity This occurs especially in alkaline solutions such as 5 per cent dextrose in water

The active component is the Nitroso group (No) which directly relaxes arteriolar and venular smooth muscles causing arteriolar and venular dilatation without mediation of autonomic nervous system[6] Reduction in peripheral vascular resistance and arterial blood pressure has been repeatedly documented with this agent The cardiac output response to nitroprusside usually depends on the pre existing circulatory state Depressed cardiac output is generally improved while there may be an actual reduction in cardiac output in patients with initially normal cardiac output and left ventricular filling pressure Alteration in heart rate is usually minimal Hemodynamic response is generally observed within two to five minutes of beginning of intravenous infusion and dissipates in about the same time after cessation of infusion Variable effects of nitroprusside on renal blood flow inulin and creatinine clearance have been observed in dogs as well as in human beings[8] With acute reduction of blood pressure in normotensive patients and those with renovascular hypertension plasma renin activity increases suggesting a possible decrease in renal perfusion[10]

Other effects of sodium nitroprusside include normalization of the square wave response of arterial pressure during Valsalva maneuver in patients with congestive heart failure (personal unpublished observations) inhibition of platelet aggregation,[11] increased intrapulmonic ventilation-perfusion mismatch with decrease in arterial Po_2 and inhibition of tension prolongation that occurs during recovery from hypoxia in isolated cat papillary muscle The last effect may prevent the incomplete relaxation thought to characterize the phenomenon of tension prolongation Improved myocardial relaxation may help in improving diastolic properties of the left ventricle with reduction in end diastolic pressure which might increase transmural myocardial blood flow

Metabolism Given intravenously nitroprusside is converted to cyanogen (see Table II) by

...ct interaction with -SH groups of erythro...es and tissues[8] Cyanogen is largely converted thiocyanate in the liver which is then removed the normal kidney with a half life of seven ...s Renal impairment may prolong thiocyanate ...ention

...nical indications

Hypertension Nitroprusside is suitable for ...pertensive emergencies including hypertension ...sociated with acute myocardial infarction and ...ronary insufficiency[1, 16] The agent promotes a ...nooth and rapid decrease in arterial blood pres...ure and its effect is rapidly reversible There is ...nerally no evidence of tachyphylaxis and ...inimal changes in heart rate

Acute myocardial infarction Recent hemody...amic studies have shown that sodium nitroprus...de improves left ventricular pump function ...uring acute myocardial infarction especially ...hen complicated by varying degrees of pump ...ailure[1] Decrease in left ventricular filling ...ressure concomitant with increased or some...times unchanged stroke volume and stroke work ...produced with little or only modest changes in ...eart rate and mean arterial pressure However a ...lecrease or no change in stroke volume is likely to ...occur in patients with normal left ventricular ...illing pressures In patients with severe pump ...ailure following acute myocardial infarction use of nitroprusside was associated with an over all ...hort term survival of 56 per cent[2] The 47 per cent survival in 17 patients with cardiogenic shock treated with ventricular unloading is superior to the expected 85 to 100 per cent mortality rate However a cumulative survival of 28 per cent at two years is probably a result of irreversible loss of myocardium Combined after load reduction with nitroprusside and increase in diastolic coronary perfusion pressure with exter nal counterpulsation in 17 patients with acute myocardial infarction five of whom were in shock was associated with significant decrease in left ventricular filling pressures and increase in stroke work[2]

In spite of the demonstrated beneficial hemo dynamic effects of nitroprusside the fall in coro nary perfusion pressure (aortic diastolic pressure) may theoretically increase myocardial ischemia and care must be taken to avoid diastolic hypo tension

Some studies using ST segment mapping to measure ischemia have shown increased evidence of ischemia with nitroprusside during acute myocardial infarction in dogs as well as humans[-, 23] whereas other studies utilizing similar techniques have not shown worsening of ischemia

Other studies have shown salutary effects of nitroprusside on the mechanical performance and metabolism of ischemic myocardium in dogs Al though no studies are available in humans to determine the effect of nitroprusside on regional myocardial ischemia and function in coronary artery disease several studies to evaluate global myocardial ischemia have not shown worsening of ischemia as measured by coronary sinus lactate levels or arterial-coronary sinus oxygen differ ence[1, 6]

The over all effect on myocardial O_2 demand and supply may depend on the relative magni tudes of decrease in wall tension and coronary perfusion pressure caused by nitroprusside and on the severity of the obstructive coronary disease

Chronic refractory congestive heart failure In patients with severe and often refractory conges tive heart failure of various etiologies i e cardio myopathy hypertensive heart disease valvular heart disease and ischemic heart disease sodium nitroprusside causes significant and sustained symptomatic improvement with decreases in left and right ventricular filling pressures and increase in stroke volume These effects are gener ally achieved with minimal changes in heart rate and modest declines in arterial pressure even in relatively hypotensive patients

REFERENCES

1. Brutsaert D L and Sonnenblick E H Cardiac muscle mechanics in the evaluation of myocardial contractility and pump function Problems, concepts and directions Progr Cardiovasc Dis 16 337 1973
2. Zelis R and Mason D T Compensatory mechanisms in congestive heart failure N Engl J Med 222 967 1970
3. Hodges M Friesinger G C Riggins R C K et al Effects of intravenously administered digoxin on mild l ft ventricular failure in acute myocardial infarction in man Am J Cardiol 29 749 1972
4. Be dek, W Forrester J S Chatterjee K et al Myocardial metabolic effect of oubain in acute myocar dial infarction Circulation 46(Suppl II) II 113 1972
5. Braunwald E Control of myocardial oxygen consump tion Physiologic and clini al considerations, Am J Cardiol 27 416 1971
6. Bagwell E E Hilliard, C C, Daniel H B et al Studies on the inotropic mechanism of phentolamine Am J Cardiol 25 83 1970
7. Braunwald E Mitral regurgitation N Engl J Med 281 425 1969

8 Palmer R F and Lasseter K C Sodium nitroprusside N Engl J Med 292 294 1975

9 Bastron R D and Kaloyanides G J Effect of sodium nitroprusside on function in the isolated intact dog kidney J Pharmacol Exp Ther 181 244 1972

10 Kaneko Y Ikeda T Takeda T et al Renin release during acute reduction of arterial pressure in normal subjects and patients with renovascular hypertension J Clin Invest 46 705 1967

11 Saxon A and Kattlove H E Platelet inhibition of sodium nitroprusside Circulation 51 (Suppl II) II 236 1975

12 Brodie T S Gray R Swan H J C and Matloff J M Effect of nitroprusside on arterial oxygenation intrapulmonic shunts and oxygen delivery Am J Cardiol 37 123 1976

13 Brodie B Chude L Klausner S Grossman W and Parmley W W Effects of sodium nitroprusside on tension prolongation during recovery from hypoxia Am J Cardiol 37 122 1976

14 Gifford R W Jr Hypertensive emergencies and their treatment Med Clin North Am 45 441 1961

15 Page I H Corcoran A C Dustan H P et al Cardiovascular actions of sodium nitroprusside in animals and hypertensive patients Circulation 11 188 1955

16 Bhatia S K and Frohlich E D Hemodynamic comparison of agents useful in hypertensive emergencies AM HEART J 85 367 1973

17 Armstrong P Walker D Benton J R et al Vasodilator therapy in acute myocardial infarction Circulation 52 1118 1975

18 Chatterjee K Parmley W W Ganz W Forrester J S Walinsky P, Crexells C and Swan H J C Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction Circulation 48 1183 1973

19 Franciosa J A Guiha N H Limes C J Rodrigues E R and Cohn J N Improved left ventricular function during nitroprusside infusion in acute myocardial infarction Lancet 1 650 1972

20 Cohn J N Vasodilator therapy of myocardial infarction N Engl J Med 290 1433 1974

21 Najam A Amsterdam E Tonkon M Vera, Z M R and Mason D T Clinical effects of nitropr[illegible] the extent of ischemic injury and pump function [illegible] myocardial infarction Circulation 52 (Suppl. II) [illegible] 1975

22 Brown T M Matthews O P, and Walter P F Assessment of effect of vasodilator therapy upon he[illegible] dynamics and ischemic injury in acute anterior myo[illegible] dial infarction Am. J Cardiol 37 1?3 19?6

23 Chatterjee K Swan H J C, Kaushik V S [illegible] Magnusson P and Forrester J S Effects of vas[illegible] lator therapy for severe pump failure in acute myoca[illegible] infarction on short term and late prognosis Circul[illegible] 53 797 1976

24 Parmley W W Chatterjee K Charuzi, Y and Swa[illegible] H J C Hemodynamic effects of non invasive sys[illegible] unloading and diastolic augmentation in patients w[illegible] acute myocardial infarction Am J Cardiol. 33 [illegible] 1974

25 Chiariello M Gold H K Leinbach R Davis, M [illegible] and Maroko P R Comparison between effects [illegible] nitroglycerin and nitroprusside on ischemic injury d[illegible] acute myocardial infarction Am J Cardiol. 37 [illegible] 1976

26 Miller R Vismara L A Williams D O Sabel [illegible] Odem R and Mason D T Effects of nitroprusside [illegible] myocardial energetics and coronary blood flow [illegible] pacing induced ischemia in patients with coronary art[illegible] disease Am J Cardiol 37 156 1976

27 Konek R Tillish J H et al Vasodilator therapy [illegible] chronic left ventricular failure Circulation 53 [illegible] 1976

28 Miller, R, Vismara L et al Clinical use of so[illegible] nitroprusside in chronic ischemic heart disease effect [illegible] peripheral vascular resistance and venous tone a[illegible] ventricular volume pump and mechanical performan[illegible] Circulation 51 328 1975

29 Guiha N H et al Treatment of refractory heart fa[illegible] with infusion of nitroprusside N Engl J Med 291 [illegible] 1974

ɔmparison of treadmill and bicycle ergometer ercise in middle aged males

ɔmparisons of bicycle and treadmill exercise tests are avail le in young adults but not for 40 to 65 year-olds who are ost frequently given exercise stress tests in clinical practice laims of advantages of one type of test over another are often ade without direct evidence a common one being that orth Americans cannot be maximally stressed with the cycle We have compared the results of maximal bicycle and eadmill tests in 305 normal males 4? to 70 years of age (mean ge 56) The Bruce protocol was used on the treadmill and on e calibrated electric bicycle ergometer subjects worked at bout 400 kpm/minute for 6 minutes immediately followed by 00 to 900 kpm/minute for six minutes after which the load as increased by 300 kpm/minute each minute with con id rable encouragement until severe fatigue Mean maximal eart rates at ages 40 to 49 50 to 59 and 60 to 69 were 179 169 nd 15? beats/minute respectively and were identical for a h ex rcise Two minutes after completion of the exercise itting heart rates were 3 per cent higher after bicycle exercise p < 01) Predicted maximal oxygen uptakes for treadmill xercise were 37 34 and 31 ml /Kg /minute for the three age groups and directly determined mean values were about 1 ml /Kg /minute below the predicted values Predicted maximal oxygen uptakes for bicycle exercise were 20 to 40 per cent below that predicted for the treadmill using the Astrand nomogram partly because the nomogram underpredicted directly measured maximal oxygen uptake values by about 20 per cent The mean maximal products of systolic blood pressure times heart rate were 7 per cent lower for treadmill exercise The mean maximal metabolic load expressed in equivalents of oxygen uptake was 6 per cent higher for treadmill work In response to a questionnaire 73 per cent of the subjects indicated preference for the treadmill test and the bi ycle test was felt to have caused more generalized fatigu more leg fatigue and was less easy to complete by about 60 per cent of the subjects

The heart rate times systolic blood pressure product was 5 per cent higher for bicycle exercise (p < 05) but the difference may have been due to problems of obtaining the pressure during maximal treadmill exercise Two bicycle tests performed one year apart gave identical measures of maximal heart rates as did two treadmill tests Two bicycle tests performed one year apart gave identical mean maximal work loads (1 315 kpm/minute) and two treadmill tests performed one year apart gave mean endurance times that were almost identical 10 9 9 7 and 8 8 minutes for the three age groups. It was concluded that both bicycle and treadmill exercises were suitable for maximal exercise tests in middle aged North American males who are not accustomed to either exercise test nor to bicycle exercise in daily life Both tests gave consistent results when performed one year apart Both tests caused similar cardiovascular distress as evidenced by equal maximal heart rates and equal systolic products Three out of four subjects preferred the treadmill exercise the three technicians involved favored using the treadmill as a test and they did not have to encourage the subjects as much There was an important difference in the predicted maximal oxygen uptake with bicycle values being well below treadmill values Predictions of aerobic power cannot be compared unless identical tests are used While the results in these normal men may not be exactly transferable to cardiac patients there seems to be little practical difference in the level of cardiac stress that can be imposed with either the treadmill or bicycle while each test has other advantages or disadvantages compared to the other

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Factors influencing the resumption of work sexual activity and driving following acute myocardial infarction

Al hough most patients who survive their first myocardial infarction should be able to resume a virtually normal life style within three to four months of the illness between 40 to 60 per cent of these patients have not returned to work by this time However this delay is rarely due to physical incapacity as a result of heart failure incapacitating angina, or dyspnea. Similarly occupations that demand an excessive physical load unsympathetic attitudes of employers or unsuitable

8 Palmer R F and Lasseter K C Sodium nitroprusside N Engl J Med **292** 294 1975

9 Bastron R D and Kaloyanides G J Effect of sodium nitroprusside on function in the isolated intact dog kidney J Pharmacol Exp Ther **181** 244 1972

10 Kaneko Y Ikeda T Takeda T et al Renin release during acute reduction of arterial pressure in normal subjects and patients with renovascular hypertension J Clin Invest **46** 705 1967

11 Saxon A and Kattlove H E Platelet inhibition of sodium nitroprusside Circulation **51** (Suppl II) II 236 1975

12 Brodie T S Gray R Swan H J C and Matloff J M Effect of nitroprusside on arterial oxygenation intrapulmonic shunts and oxygen delivery Am J Cardiol **37** 123 1976

13 Brodie B Chude L Klausner S Grossman W and Parmley W W Effects of sodium nitroprusside on tension prolongation during recovery from hypoxia Am J Cardiol **37** 122 1976

14 Gifford R W Jr Hypertensive emergencies and their treatment Med Clin North Am **45** 441 1961

15 Page I H Corcoran A C Dustan H P et al Cardiovascular actions of sodium nitroprusside in animals and hypertensive patients Circulation **11** 188 1955

16 Bhatia S K and Frohlich E D Hemodynamic comparison of agents useful in hypertensive emergencies Am Heart J **85** 367 1973

17 Armstrong P Walker D Benton J R et al Vasodilator therapy in acute myocardial infarction Circulation **52** 1118 1975

18 Chatterjee K Parmley W W Ganz W Forrester J S Walinsky P Crexells C and Swan H J C Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction Circulation **48** 1183 1973

19 Franciosa J A Guiha N H Limes C J Rodrigues E R and Cohn J N Improved left ventricular function during nitroprusside infusion in acute myocardial infarction Lancet **1** 650 1972

20 Cohn J N Vasodilator therapy of myocardial infarction N Engl J Med **290** 1433 1974

21 Najam A Amsterdam E Tonkon M Vera Z L R and Mason D T Clinical effects of nitrop[illegible] the extent of ischemic injury and pump function [illegible] myocardial infarction Circulation **52** (Suppl II) II 1975

22 Brown T M Matthews O P and Walter P F Assessment of effect of vasodilator therapy upon he[illegible] dynamics and ischemic injury in acute anterior myo[illegible]dial infarction Am J Cardiol **37** 1?3 19?6

23 Chatterjee K Swan H J C Kaushik V S Joh[illegible] Magnusson P and Forrester J S Effects of va[illegible]lator therapy for severe pump failure in acute myoc[illegible] infarction on short term and late prognosis Circ[illegible] **53** 797 1976

24 Parmley W W Chatterjee K Charuzi Y and Sw[illegible] H J C Hemodynamic effects of non invasive sys[illegible] unloading and diastolic augmentation in patients w[illegible] acute myocardial infarction Am J Cardiol 33[illegible] 1974

25 Chiariello M Gold H K Leinbach R Davis M[illegible] and Maroko P R Comparison between effects [illegible] nitroglycerin and nitroprusside on ischemic injury d[illegible] acute myocardial infarction Am J Cardiol 37[illegible] 1976

26 Miller R Vismara L A Williams D O S[illegible] Odem R and Mason D T Effects of nitroprusside [illegible] myocardial energetics and coronary blood flow d[illegible] pacing induced ischemia in patients with coronary he[illegible] disease Am J Cardiol **37** 156 1976

27 Konek R Tillish J H et al Vasodilator therap[illegible] chronic left ventricular failure Circulation 53[illegible] 1976

28 Miller R Vismara L et al Clinical use of so[illegible] nitroprusside in chronic ischemic heart disease effec[illegible] peripheral vascular resistance and venous tone [illegible] ventricular volume pump and mechanical perf[illegible] Circulation **51** 328 1975

29 Guiha N H et al Treatment of refractory heart fa[illegible] with infusion of nitroprusside N Engl J Med 291[illegible] 1974

xperimental conditions also occur following prolonged environmental stress Resolution of this issue has waited on the development of valid epidemiologic techniques and reliable instruments to measure environmental stress These strategies are rapidly advancing and appear to confirm the relationship between stressful life events and cardiovascular disease As the physiologic response to acute experimental stress the occurrence of disease in response to environmental stress is neither specific nor inevitable Almost any disease may be associated with an increase in recent life events including psychiatric medical and surgical diseases Epidemiologic evidence has shown an increased incidence of hypertension in air traffic controllers, but this study also demonstrated that many individuals did not succumb and that others developed ulcer or diabetes rather than hypertension

This individual variability in response to environmental stress may be accounted for by genetic variables the presence of contributory risk factors (such as smoking diet or obesity) or by differences between people in how they respond psychologically to stress However when genetic factors are held constant in studies on monozygotic twins stress factors remain important in the etiology of cardiovascular conditions

Psychological responses to stress

Individuals exposed to identical stress respond psychologically in widely differing ways This variability is based on characteristics that are described in a number of ways as coping devices personality traits psychological defenses, or resistance resources These different terminologies have been used in attempts to couple specific personal characteristics to particular disease states In hypertension Franz Alexander maintained that high blood pressure was contributed to by suppressed emotional conflict particularly aggressive or hostile impulses A more recent attempt at stereotypy has been the Type A personality described as impatient fast moving and also aggressive Such stereotypes are not observed in every individual with hypertension and are not identifiable in all cultures including some where cardiovascular disease is rampant (such as Holland) All the terms that attempt to describe predictable behavior responses to stress can be summarized as an inability to adapt to change As Theorell has pointed out Whether this defective ability should be called 'Type A Behavior Sisyphus syndrome work addiction or neuroticism and whether we are dealing with genetic traits or behavior patterns formed by early childhood circumstances is not known

The safest conclusion is that stress and change can provoke disease in some genetically predisposed individuals who have defects in psychological adaptation to change Paradoxically it may be this defect in psychological adaption that actually results in the detection of the disease to an over representation of the association between physical and psychological factors and to the assumption of a causal relationship This is particularly so in hypertension because it is a silent disease Cases are discovered very often in patients who make somatic complaints in response to psychosocial stress including such symptoms as headaches, lassitude or tension In such individuals high blood pressure is often discovered accidentally on routine physical examination. This response of some individuals to stress has been called illness behavior It is more common in people with poor emotional vocabularies who enlist psychological aid from the physician through the medium of physical complaints. Such individuals may also value being cared for highly

In clinical practice populations of patients with hypertension are therefore likely to contain an over representation of individuals poor at coping with stress, in some of whom this factor may indeed have a part to play in causation or aggravation of the disease (along with other genetic and risk factors) In contrast hypertensives discovered through routine screening programs will contain fewer individuals in whom psychological factors are an important component but in whom other risk factors may predominate This is supported by epidemiologic surveys using measures of "anxiety or "hostility which have shown no difference between individuals with previously undetected blood pressure and normal controls.

Medication

Dissatisfaction with existing hypotensive drugs and their side effects is manifested by a non adherence rate in several studies of up to 50 percent Patients with concurrent anxiety and hypertension often self medicate with alcohol or are prescribed minor tranquilizers Sixteen percent of the 60 million annual prescriptions for diazepam are prescribed to patients with cardiovascular disease A recent survey of our own in a hypertension clinic revealed that 40 percent of patients were taking a minor tranquilizer This is over twice the national rate for age and sex comparable groups Moreover a majority of patients treated with minor tranquilizers are dissatisfied with this means of chemical coping and feel it is not the best way of dealing with stress

Identified hypertensives are therefore a group of patients in whom problems at coping with stress are frequent and these are poorly treated along with the disease itself

Meditation

The probability that inadequate response to stress is one risk factor in hypertension that it is over represented in the clinical population and inadequately treated suggests a place for other methods of psychological intervention As has been pointed out to the extent that people have modest aspirations and less intense commitments they more easily insulate themselves from stress Most physicians are aware of this when they advise cardiovascular patients to "take it easy Unfortunately individual motivations and social pressures make such advice easier to give than to take What most people seek is some technique by which they can enhance their adaptation to existing life conditions without reducing their commitments That Transcendental Meditation (TM) offers precisely this is reflected in the title of its latest book Discovering Inner Energy and Overcoming Stress In a forward to this book, Hans Selye himself writes that TM "can help humanity face the crises of modern life" Since this book was 9 weeks on the best seller list most physicians must now have been called on to deal with patients who are seeking advice or referral concerning meditation

Meditational techniques can be traced through the ages in most religions and many have marked similarities to TM Common components of most meditational techniques are a quiet environment relaxed posture passive attitude and use of a repetitive phrase or word (called the mantra in TM) the purpose of which is to shift thought inward and away from logical, externally oriented concern In more modern times, such techniques have included progressive muscle relaxation

transport facilities are relatively unusual causes for an inappropriately slow rehabilitation Frequently patients who delay or fail to resume work and a normal life style do so without apparent reason Psychological factors have often been considered to be the major determinant of a successful or unsuccessful rehabilitation However such reasoning has usually been based on theoretical considerations subjective impressions or clinical observation of small samples rather than reflecting the findings of well controlled studies

Recently investigations have been conducted to assess the relative influence of medical occupational psychological and social factors on various aspects of rehabilitation following acute myocardial infarction In the first study 112 patients were reviewed Delay in returning to work within four months of leaving hospital was more frequent among those patients who were either not given early hospital follow up appointments or who had attributed their illness to aspects of their work Encouragement by general practitioners to resume employment was found to be almost essential if an undue delay was to be avoided and it would appear that positive advice of this nature was likely to be given more frequently if patients had already attended early hospital review Age neuroticism personal knowledge of how others had fared following a similar illness and benefits from sickness payments do not seem to influence the rate of return to work

An assessment of the relative influence of detailed pre discharge medical counselling on rehabilitation was made of 35 patients admitted with their first acute myocardial infarction The rate of resumption of work sexual activity and car driving was compared with similar observations in a controlled group of patients who had not received any formal pre discharge medical guidance At the four month follow up it was observed that similar proportions of patients in the two groups had resumed these activities Therefore it was concluded that this form of medical counselling was unlikely to influence the course of rehabilitation as measured by the above parameters of behavior It was again noted however that encouragement by the general practitioner was likely to prove helpful

In another study similar indices of rehabilitation (resumption of work sexual activity and car driving) were examined four and 10 months after leaving hospital in 32 patients who had survived primary ventricular fibrillation following their first myocardial infarction When compared with co patients whose first infarct was not so complicated and the the early mortality rate was similar it was noted that at 4 months a significantly smaller percentage of the ventric fibrillation group had achieved a satisfactory level of rehabilitation However by 10 months this difference had disappeared In both groups age and the type of occupation w found to be the most influential factors in determining wh patients would return to work within 10 months

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REFERENCES

1 World Health Organisation Rehabilitation of patien with cardiovascular diseases WHO Technical Rep Series No 270 1964
2 Myocardial Infarction—How to prevent—How to rehab itate Sponsored by the Council on Rehabilitation I national Society of Cardiology 1973
3 Croog S H Levine S and Lurie Z The heart pa and the recovery process A review of the direction of research on social and psychological factors Soc Sc Med 2 111 1968
4 Kushnir B Fox K M Tomlinson I W Portal R W and Aber C P The influence of psychological fa and an early hospital follow up on return to work a first myocardial infarction Scand J Rehab Med 7 1975
5 Kushnir B Fox K M Tomlinson I W and Aber C P *The effect of a predischarge consultation on the resumption of work sexual activity* and driving follow ing *acute myocardial infarction* Scand J Rehab Med (In press 1976)
6 Kushnir B Fox K M Tomlinson I W Portal R W and Aber C P Primary ventricular fibrillation and resumption of work sexual activity and driving after *first acute myocardial infarction Br* Med J 4 60 1975

Hypertension Medicate or meditate?

Once the sphygmomanometer was invented and hypertension was recognized as the most common chronic disease blood pressure became an obvious and observable end point for physiologists physicians and psychologists interested in the mind-body interaction and models to examine it For almost a century there has been constant speculation on the relation ship between life stress the individual s response and blood pressure changes

Stress personality and blood pressure

Popular acceptance that stress plays a possible role in the etiology or aggravation of hypertension followed in the wake of Cannon s flight or fight hypothesis and Selye s enuncia tion of a General Adaptation Syndrome"

The fact that short term psychologic stress can provoke physiologic change is well proven including the observation that individuals differ in which physiologic variable is most altered (pulse rate skin resistance respiration or blood pressure) Between one third and two thirds of individual show a reproducible response stereotype to stress. It has also been shown that identified hypertensives exposed to stress display the predictable response stereotype of increased blood pressure The still incompletely answered question is the extent to which changes that take place under acute

ernmental conditions also occur following prolonged envi mental stress Resolution of this issue has waited on the elopment of valid epidemiologic techniques and reliable truments to mea ure environmental stress These strategies rapidly advancing and appear to confirm the relationship ween stressful life events and cardiovascular disease As h the physiologic response to acute experimental stress the urrence of disease in response to environmental stress is ther pecific nor inevitable Almost any disease may be ociated with an increase in recent life events including ychiatric medical and surgical di eases Epidemiologic dence has shown an increased incidence of hypertension in traffic controllers but this study also demonstrated that iny individuals did not succumb and that others developed er or diabetes rather than hypertension

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Individuals exposed to identical stress respond psychologi lly in widely differing ways This variability is based on aracteristics that are described in a number of ways as oping devices" personality traits" psychological de nses or resistance resources These different terminol gies have been used in attempts to couple specific personal aracteristics to particular disease states In hypertension ranz Alexander maintained that high blood pressure was ontributed to by suppressed emotional conflict particularly ggressive or hostile impulses A more recent attempt at ereotypy has been the Type A personality described as mpatient fast moving and also aggressive Such stereotypes re not observed in every individual with hypertension and are ot identifiable in all cultures, including some where cardio ascular disease is rampant (such as Holland) All the terms hat attempt to describe *predictable behavior* responses to tress can be summarized as an inability to adapt to change As Theorell has pointed out Whether this defective ability should be called Type A Behavior Sisyphus syndrome work addiction or neuroticism *and whether* we are dealing with genetic traits or behavior patterns formed by early childhood circumstances is not known

The safest conclusion is that stress and change can provoke disease in some geneti ally predi posed individuals who have d fects in psychological adaptation to *change Paradoxically* it may be this defect in psychological adaption that actually results in the detection of the disease to an over representa tion of the association between physical and psychological factors and to the assumption of a causal relationship This is particularly so in hypertension because it is a silent disease Cases are discovered ery often in patients who make somatic compla nt in response to psychosocial stres including such symptoms as headaches lassitude or tension In such individ uals, h gh blood pressure is often discovered accidentally on routine phy i al examination This re ponse of some individ uals to stress has been called illness beha ior It is more common in people with poor emotional vocabularies who enli t psychological aid from the physician through the medium of physical complaints Such individuals may also value being cared for highly

In clinical practice populations of patients with hyperten sion are therefore likely to contain an over representation of individuals poor at coping with stress in some of whom this factor may indeed have a part to play in causation or aggravation of the disease (along with other genetic and risk factors) In contrast hypertensives discovered through routine screening programs will contain fewer individuals in whom psychological factors are an important component but in whom other risk factors may predominate This is supported by epidemiologic surveys using measures of anxi ety or hostility which have shown no difference between individuals with previously undetected blood pres ure and normal controls

Medication

Dissatisfaction with existing hypotensive drugs and their side effects is manifested by a non adherence rate in several studies of up to 50 percent Patients with concurrent anxiety and hypertension often self medicate with alcohol or are prescribed minor tranquilizers Sixteen percent of the 50 million annual prescriptions for diazepam are prescribed to patients with cardiovascular disease A recent survey of our own in a hypertension clinic revealed that 40 percent of patients were taking a minor tranquilizer This is over twice the national rate for age and sex comparable groups Moreover a majority of patients treated with minor tranquil izers are dissatisfied with this means of chemical coping and feel it is not the best way of dealing with stress

Identified hypertensives are therefore a group of patients in whom problems at coping with stress are frequent and these are poorly treated along with the di ease itself

Meditation

The probability that inadequate response to tress is one risk factor in hypertension that it is over represented in the clinical population and inadequately treated suggests a place for other methods of psychological intervention As has been pointed out to the extent that people have modest a pira tions and less intense commitments they more easily insulate themselves from stress Most physicians are aware of this when they advise cardiovascular patients to take it easy Unfortunately individual motivations and social pressures make such advice easier to give than to take What most people seek is some technique by which they can enhance their adaptation to existing life conditions without reducin their commitments That Transcendental Meditation (TM) offers precisely this is reflected in the title of its latest book, Discovering Inner Energy and Overcoming Stress " In a forward to this book Hans Selye himself writes that TM "can help humanity face the crises of modern life Since this book was 25 weeks on the best seller list most physicians must now *have been called* on to deal with patients who are seeking advice or referral concerning meditation

Meditational techniques can be traced through the ages in most religions and many have marked similarities to TM Common components of most meditational techniques are a *quiet environment* relaxed posture passive attitude and use of a repetitive phrase or word (called the mantra in TM) the purpose of which is to shift thou ht inward and away from logical externally oriented concerns In more modern times such techniques have included progressive *muscle* relaxation

transport facilities are relatively unusual causes for an inappropriately slow rehabilitation Frequently patients who delay or fail to resume work and a normal life style do so without apparent reason Psychological factors have often been considered to be the major determinant of a successful or unsuccessful rehabilitation[2] However such reasoning has usually been based on theoretical considerations subjective impressions or clinical observation of small samples rather than reflecting the findings of well controlled studies

Recently investigations have been conducted to assess the relative influence of medical occupational psychological and social factors on various aspects of rehabilitation following acute myocardial infarction In the first study 112 patients were reviewed Delay in returning to work within four months of leaving hospital was more frequent among those patients who were either not given early hospital follow up appointments or who had attributed their illness to aspects of their work Encouragement by general practitioners to resume employment was found to be almost essential if an undue delay was to be avoided and it would appear that positive advice of this nature was likely to be given more frequently if patients had already attended early hospital review Age neuroticism personal knowledge of how others had fared following a similar illness and benefits from sickness payments do not seem to influence the rate of return to work

An assessment of the relative influence of detailed pre discharge medical counselling on rehabilitation was made of 35 patients admitted with their first acute myocardial infarction The rate of resumption of work sexual activity and car driving was compared with similar observations in a controlled group of patients who had not received any formal pre discharge medical guidance At the four month follow up it was observed that similar proportions of patients in the two groups had resumed these activities Therefore it was concluded that this form of medical counselling was unlikely to influence the course of rehabilitation as measured by the above parameters of behavior It was again noted however that encouragement by the general practitioner was likely to prove helpful

In another study similar indices of rehabilitation (resumption of work sexual activity and car driving) were examined four and 10 months after leaving hospital in 32 patients who had survived primary ventricular fibrillation following their first myocardial infarction When compared with co[illegible] patients whose first infarct was not so complicated and [illegible] the early mortality rate was similar it was noted that a[illegible] months a significantly smaller percentage of the ve[illegible] fibrillation group had achieved a satisfactory level of reh[illegible] itation However by 10 months this difference had d[illegible] peared In both groups age and the type of occupation [illegible] found to be the most influential factors in determining [illegible] patients would return to work within 10 months

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REFERENCES

1 World Health Organisation Rehabilitation of patie[illegible] with cardiovascular diseases WHO Technical Rep[illegible] Series No 270 1964
2 Myocardial Infarction—How to prevent—How to reh[illegible] itate Sponsored by the Council on Rehabilitation, In[illegible] national Society of Cardiology 1973
3 Croog S H Levine S and Lurie Z The heart pa[illegible] and the recovery process A review of the direction[illegible] research on social and psychological factors Soc Sci Med 2 111 1968
4 Kushnir B Fox K M Tomlinson I W Portal R [illegible] and Aber C P The influence of psychological fac[illegible] and an early hospital follow up on return to work [illegible] first myocardial infarction Scand J Rehab Med 7 1975
5 Kushnir B Fox K M Tomlinson I W and Aber C P The effect of a predischarge consultation on the resumption of work sexual activity and driving fo[illegible] ing acute myocardial infarction Scand J Rehab Med (In press 1976)
6 Kushnir B Fox K M Tomlinson I W Portal R W and Aber C P Primary ventricular fibrillation a[illegible] resumption of work sexual activity and driving after first acute myocardial infarction Br Med J 4 6[illegible] 1975

Hypertension Medicate or meditate?

Once the sphygmomanometer was invented and hypertension was recognized as the most common chronic disease blood pressure became an obvious and observable end point for physiologists physicians and psychologists interested in the mind-body interaction and models to examine it For almost a century there has been constant speculation on the relationship between life stress the individual s response and blood pressure changes

Stress personality and blood pressure

Popular acceptance that stress plays a possible role in the etiology or aggravation of hypertension followed in the wake of Cannon s flight or fight hypothesis and Selye s enunciation of a General Adaptation Syndrome

The fact that short term psychologic stress can provoke physiologic change is well proven including the observation that individuals differ in which physiologic variable is most altered (pulse rate skin resistance respiration or blood pressure) Between one third and two thirds of individuals show a reproducible response stereotype to stress It has also been shown that identified hypertensives exposed to stress display the predictable response stereotype of increased blood pressure The still incompletely answered question is the extent to which changes that take place under acute

Lacey J I Bateman D E and Van Lehn R Autonomic response specificity An experimental study Psychosom Med 15 8 1953
Engel, B T and Bickford A F Response specificity Stimulus response and individual response specificity in essential hypertensives Arch Gen Psychiatry 5 4 8 1961
Gutmann M C and Benson H Interaction of environmental factors and systemic arterial blood pressure A review Medicine 50 543 1971
Dohrenwend B S and Dohrenwend B P Stressful life events New York 1974 John Wiley and Sons Inc
Rahe R H and Lind E Psychosocial factors and sudden cardiac death A pilot study J Psychosom Res 5 9 19 1
Rahe R H and Paa ikivi J Psychosocial factors and myocardial infarction II An outpatient study in Sweden J Psychosom Res 15 33 1971
Theorell T and Rahe R H Psychosocial factors and myocardial infarction I An inpatient study in Sweden J Psychosom Res 15 25 1971
Edwards M K Life crisis and myocardial infarction Master of Nursing Thesis University of Washington Seattle 1971
Holmes T H and Masuda M Life change and illness susceptibility in Dohrenwend B S and Dohrenwend B P eds Stressful life events New York 19 4 John Wiley and Sons, Inc
Cobb S and Rose R M Hyperten ion peptic ulcer and diabetes in air traffic controllers J A M A 224 489 1973
Liljefors, L and Rahe R H An identical twin study of psychosocial factors in coronary heart disease in Sweden Psychosom Med 32 523 19 0
Alexander F Psychosomatic medicine New York 1950 W W Norton pp 143 153
Friedman M and Rosenman R H Type A behavior and your heart Greenwich Conn 1974 Fawcett Publications, Inc
Theorell T Life events before and after the onset of a premature myocardial infarction in Dohrenwend B S and Dohrenwend B P eds Stressful life events New York 19 4 John Wiley and Sons Inc chapter 6
Mechanic D and Volkart E H Stress illness behavior and the sick role Am Social R v 26 51 1961
Wooley S C Blackwell B A behavioral probe into social contingencies on a psychosomatic ward J Appl Behavioral Anal 8 337 1975
9 Cochrane R Hostility and neuroticism among unselected essential hypertensives J Psychosom Res 17 215 1973
20 Blackwell B Drug therapy Patient compliance N Engl J Med 289 249 19 3
21 Blackwell B "Enhancing Compliance with Therapeutic Regimens Paper presented at the First International Congress on Patient Counseling Amsterdam 1976
22 Blackwell B Minor tranquilizers Use misuse or over use? Psychosomatics 16 28 1975
23 Manheimer D I Davidson S T Balter B B Mellinger G D Cisin I H and Parry H J Popular attitudes and beliefs about tranquilizers Am J Psychiatry 130 1246 1973
24 Mechanic D Discussion of research programs on relations between stressful life events and episodes of physical illness in Dohrenwend B S and Dohrenwend B P eds Stressful life events New York 1974 John Wiley and Sons Inc chapter 5
25 Bloomfield H Cain M Jaffe D and Kory R TM Discovering inner energy and overcoming stress New York 1975 Dell Publishing Co Inc
26 Allison J Respiration changes during transcendental meditation Lancet 1 833 19 0
27 Wallace R K Physiological effects of transcendental meditation, Science 167 1751 1970
28 Woolford R L Psychophysiological correlates of meditation Arch Gen Psychiatry 32 13 6 19 5
29 Patel C Twelve month follow up of Yoga and biofeedback in the management of hypertension Lancet 1 62 19 5
30 Stone R A and DeLeo J Psychotherapeutic control of hypertension N Engl J Med 294 80 1976
31 Benson H Rosner B A Marzetta B R and Klemchuk H P Decreased blood pressure in borderline hypertensive subjects who practiced meditation J Chronic Dis 27 163 1974
32 Benson H Rosner B A Marzetta B R and Klemchuk H P Decreased blood pressure in pharmacologically treated hypertensive patients who regularly elicited the relaxation response Lancet 1 89 19 5
33 Blackwell B Hanenson I Bloomfield S., Megenheim H Gartside P Nidich S Robinson A and Zigler R Transcendental Meditation in hypertension Individual response patterns Lancet 1 223 19 6
34 Benson H The relaxation response New York 1975 William Morrow & Co
35 Ayman D An evaluation of therapeutic results in hypertension J.A.M.A 95 246 1930
36 Shapiro A P Consideration of multiple variables in evaluation of hypotensive drugs J A M A 160 30 1956

Of what much of this is about

Money

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autogenic training hypnosis Zen and Yoga TM is a derivative of Yoga taught and proselytized by Maharishi Maresh Yogi who introduced it from India to the United States in 1959 Since then the movement has grown to where there are over an estimated 6 000 teachers and close to half a million meditators as well as a university dedicated to the Science of Creative Intelligence Individuals who undertake TM are instructed by qualified teachers at a cost of 125 dollars given a personal mantra and after learning to meditate they practice the technique for twenty minutes twice daily

Evidence for physiologic changes associated with meditation was first reported from studies on Yogis in India followed by research in Europe and America There have now been six well designed laboratory studies on TM showing consistent physiologic changes including slowing of the EEG increased skin resistance and decreased oxygen consumption These changes are quite different from those observed in either sleep or hypnosis A recent review of this research drew attention to design flaws that made it difficult to identify the specific and dependent variables in causal relationships that account for meditative phenomena Woolford stated that this was due in part to a complex framework of expectation philosophical belief and social influence

Particular effects on blood pressure have been reported with several types of meditational technique including Yoga relaxation therapy and TM These studies all report significant and clinically meaningful reductions in blood pressure Degree of control and research design has varied but most have been within subject designs using extended base lines to limit the effects of focused attention One study showed significant results compared to a control group of matched hypertensives told to rest on a couch

In our own study seven selected hypertensives were stabilized on drugs at a research clinic After they had learned TM they were seen weekly and also took their own blood pressures several times daily After twelve weeks of TM six subjects showed psychologic changes and reduced anxiety scores Six subjects also showed significant reductions in home and four in clinic blood pressures Six months later the subjects continued to derive psychologic benefits and two showed significant blood pressure reductions attributable to TM both at home and in the clinic It is also important to note that the subjects who failed to benefit from TM subsequently obtained relief in both psychologic complaints and increased blood pressure after reverting to more conventional methods of treatment In addition one individual found recording his own blood pressure was unsettling and another ceased meditation because although it appeared helpful it was not worth 40 minutes a day of his time

Considered together these results indicate that most intelligent motivated subjects derive some psychological benefit from TM a minority shows sustained benefit in blood pressure some show transistory benefit and others show none The presence of psychological benefit the absence of drug side effects and the experience of self control may make TM an appealing therapeutic adjunct for some hypertensive individuals Others may find the time commitment mystical aspects payment of a fee and assumption of personal responsibility less appealing

The question of the specificity of the affects attributable to TM remains doubtful in both the clinical and laboratory experiments This is a subject of controversy among teachers of meditation themselves strict advocates of TM aver that only its precise technique is safe and effective while others are convinced that a form of "relaxation response" alone is quite sufficient Ironically but not too surprisingly the scientists who originated the earliest scientific research now sit on opposite sides of this theoretical fence

At a more important level none of the studies on blood pressure have applied a meaningful control for the interest or mystique of meditation In this regard it is relevant to reflect on the impact of non specific variables on some patients who experience problems in coping with stress In 1930 Ayman conducted a review of over 30 studies on the therapeutic effects of the many nostrums used to treat hypertension before modern drugs became available Treatments such as dilute hydrochloric acid and liver extract produced marked relief of symptoms such as headache or lassitude that are commonly regarded as psychosomatic This led Ayman to conclude his review as follows "On the basis of these reports it may therefore be concluded that the symptoms associated with hypertension are easily relieved that they are more easily relieved than the blood pressure is lowered and that this may be obtained by the use of numerous drugs or methods." Somewhat similar conclusions were arrived at by Shapiro following a detailed review of non pharmacologic influences on blood pressure and methods of treating it

Advice to the patient

Treatment in medicine seldom waits on proof The causes of hypertension are uncertain the efficacy of drugs unproved in mild uncomplicated cases and the validity of most risk factors remains in doubt But preventative action in fatal disease is wise at probability levels below five per cent particularly if prophylaxis can be accomplished effectively at low risk TM is therefore one more therapy that deserves consideration as an adjunct in the management of hypertension Physicians serve a dual function in making patients aware of what help is available while protecting them from panaceas Medical compassion should be tempered with scientific skepticism The benefits of TM are real but sometimes temporary in duration and perhaps nonspecific in origin TM is not for everybody Any patient who asks for advice about TM has already taken a step toward recognizing that stress and coping with it may be significant factors in his disease This alone deserves discussion that may lead not necessarily or only to meditation but to modification of life style and changes in personal behavior that may reduce one of the major risk factors in this complex disease and its fatal complication

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REFERENCES

1 Cannon W B The emergency function of the adrenal medulla in pain and the major emotions Am J Physiol 33 356 1914
2 Selye H The stress of life New York 1956 McGraw Hill Book Company Inc

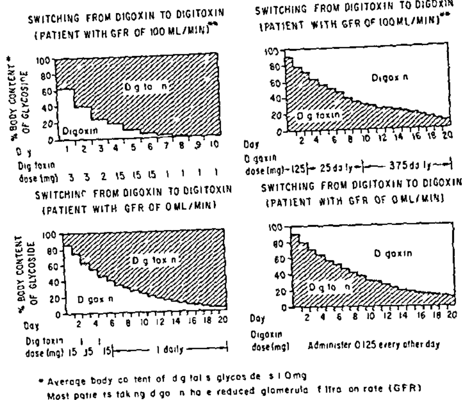


Fig 1 Changing digitalis glycosides in an average size adult For explanation see text

from digoxin to digitoxin or vice versa This switch is to be accomplished without altering the total level of digitalization of the patient

Data taken from the literature were used to calculate elimination rates for digoxin and digitoxin in patients with normal renal function and no renal function Calculated doses that would maintain a constant total body glycoside content while changing drugs and the ratios of digoxin to digitoxin in the patient at any time during the changeover period are presented in Fig 1 Digoxin dosage for patients whose renal function is moderately impaired can be extrapolated from the values given Individualization of glycoside dose would be required for those patients who do not have average elimination rates or do have unusual drug sensitivity

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REFERENCES

1 Jusko W J Szetler S J and Goldfarb A L Pharmacokinetic design of digoxin dosage regimens in relation to renal function J Clin Pharmacol 14 5_ 19 4
2 Reuning R H Sams P A and Notari R E Role of pharmacokinetics in drug dosage adjustment I Pharmacologic effect kinetics and apparent volume of distribution of digoxin J Clin Pharmacol 13 127 19 3
3 Jelliffe R W Administration of di oxin Dis Chest 56 56 1969
4 Dettli L Individualization of drug dosage in patients with renal disease Med Clin North Am 58 977 1974
5 Smith T W Digitalis glycosides N Engl J Med 288 /1 1973
6 Smith, T W Radioimmunoassay for serum digitoxin concentration methodology and clinical experience J Pharmacol Exp Ther 175 35 1970
7 Rasmussen K Jervell J Storstein L et al Digitoxin kinetics in patients with impaired renal function Clin Pharmacol Ther 13 6 19 ?

Soup—the right recipe

To the Editor

It takes time and the ri ht ingredients to make a good soup That's why as Dr Neumann writes "Rarely is soup nowadays truly home made " (AM HEART J 9? 266 1976) For obvious reasons there is less time these days for home cooking But why shouldn t industrially prepared soups be as wholesome and healthy as those made at home? The commercial soup manufacturers have at their disposal all the ingredients and time necessary to produce nourishing and good tasting soups. Why are taste enhancers necessary when truly

Letters to the Editor

Dopamine and blood flow

To the Editor

Dopamine was described as a vasoconstrictor of intestinal circulation in a recent paper in the AMERICAN HEART JOURNAL (Pawlik W, Mailman D, Shanbour L L, and Jacobson E D: Dopamine effects of the intestinal circulation. AM HEART J 91 325, 331 1976). We believe all the doses employed by these investigators to be excessive and that the direct specific dopaminergic vasodilation in the intestinal circulation was masked by the alpha adrenergic vasoconstriction of dopamine manifest at very high doses.

The author's dogs weighed 15 to 23 kilograms and we would estimate their cardiac output to be about 2.5 liters/min. The intestinal segments perfused weighed 81 Gm with a blood flow of 2.5 ml/min. Thus blood flow of the perfused intestine amounted to about 1 per cent of the cardiac output. The effects of dopamine are dissipated rapidly and little would recirculate to the perfused intestine—thus most of the effects would be due to the dopamine present during the first circulation. Indeed the authors observed no systemic effects of dopamine perfused in this manner.

At the lowest dose employed, 1 μg/Kg/min, the local effects would be equivalent to intravenous administration of 100 times this dose, as the total systemic blood flow was about 100 times the blood flow to the isolated intestinal segment into which dopamine was infused directly. This dose is about 50 times greater than the usual initial dose in dogs or patients and will produce systemic, renal and mesenteric vasoconstriction in all dogs. The intermediate dose employed, 5 μg/Kg/min, would be equivalent to 500 μg/Kg/min given intravenously—about the maximum dose that would ever be used clinically even in the most refractory patient in shock. The largest dose employed, 20 μg/Kg/min, would be equivalent to giving 1008 ampules of drug each day to a 70 kilogram patient!

Studies in our laboratory in dogs clearly demonstrate the dopaminergic vasodilation of intestinal circulation. Electromagnetic flow probes are placed on the superior mesenteric artery and dopamine is injected into a small side branch of this vessel. The maximum vasodilation, an average decrease of mesenteric vascular resistance of 24 per cent, occurs with a dopamine infusion rate 15 per cent of the smallest dose employed by Dr. Pawlik and his colleagues.

The use of multiple doses to define pharmacological activity is essential, but they must also encompass the range of all actions of the drug. Initial studies of dopamine a half century ago employed excessive doses and concluded it was a vasoconstrictor similar to norepinephrine, its metabolite. Only when Leon Goldberg performed careful dose-response studies of dopamine did its unique specific vasodilating actions become known. I suggest that Dr. Pawlik and his colleagues continue their careful studies, extending the doses of dopamine to the range of 0.01 to 0.5 μg/Kg/min.

If a blind man ventured out to describe an elephant and on his first experience had the elephant sit upon him, his image of the elephant would be somewhat different than that of the artist who palpated all parts of the beast.

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Reply

To the Editor

The letter by Drs. Thompson and Bloxham criticizes our recent paper (AM HEART J 91 325, 1976) on several grounds. First, they object to our use of large doses of dopamine infused intra-arterially into a branch of the superior mesenteric artery and imply that we are ignorant of the dilator effect of dopamine at lower doses. In the paper we stated twice in the introduction and once in the discussion that lower doses of dopamine are vasodilator in this circulation. If we choose to explore the constrictor effects of higher doses, that after all is our prerogative.

Drs. Thompson and Bloxham criticize our failure to block dopaminergic effects using alpha adrenergic as well as beta adrenergic antagonists. Such studies were performed and reported in an earlier paper by one of the authors (Can J Physiol Pharmacol 50 594 602, 1972) and is referenced in the text of our recent publication.

Drs. Thompson and Bloxham indicate that preliminary work in their laboratory indicates that infusion of dopamine at a dose of 1/10 of the lowest that we had reported evoked a 24 per cent decrease in mesenteric vascular resistance. Recently we infused dopamine for 10 minutes into a branch of the superior mesenteric artery at a dose 1/10 of the lowest that we had reported and we found a 19 per cent increase in blood flow at 1 minute, which faded to a 10 per cent increase at 5 minutes and a 5 per cent increase at 10 minutes after start of the continuous dopamine infusion. This is not the mark of a terribly potent vasodilator drug, contrasted with the infusion of glucogon, isoproterenol or prostaglandin E, for example (Gastroenterology 62 39, 1972).

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Changing digitalis glycosides in an average size adult

To the Editor

One of the problems occasionally encountered in practice is how to change the digitalis glycoside being taken by a patient

ent Ad ances in Studies on Cardiac Structure and Metab sm Vol 9 The Sarcolemma *Edited by* Paul Emile Roy 1 N S Dhalla (Series Editor G Rona) Baltimore 19 6 University Park Press 490 pages $29 50

This is another excellent volume in the series related to rdiac structure and metabolism The sarcolemma has been own to be an important structure of the myocyte However is book reviews extensively the structure biophysics and nction of this important membrane The many contributors om all over the world discussed in detail in Quebec during ne 19 4 the sarcolemma of the myocardium The biochem try pathophysiology and normal physiology and structure the sarcolemma are rather exhaustively and clearly viewed in this 490 page book This is an excellent book on a ngle important cell membrane

fective Endocarditis Edited by Donald Kaye Baltimore 9 6 *University Park Press* 272 pages $19 50

This book edited by Donald Kaye contains a series of papers n various aspects of infective endocarditis The papers iclude definition epidemiology etiology infecting organisms lin cal manifestations use of prosthetic valves diagnosis and ntibiotic treatment This one volume reviews in a single ource the clinical problems of bacterial endocarditis It epresents a thorough review of the subject and includes iscussions of some of the difficult problems encountered in atients The bibliography included with each chapter is seful for readers who wish to extend the study of this mportant problem This is a useful and very good book on the subject

Advances in Non nvas ve D agnostic Card ology Edited by Benedict Kingsle Sc D Joseph W Linhart M D and Philip Kantrowitz Sc D Thorofare N J 19 6 Charles B Slack, Inc 233 pages

This book is more of an atlas than a text It reviews the present status of exercise testing phonocardiography echo cardiography prosthetic devices and miscellaneous procedures such as *apexcardiography* nuclear cardiology Doppler tracings plethysmography and others Some of these discussions are not critically presented although the book does review the methods very well from the point of view of present day practice Physicians and trainees will find the *book to be useful and a stimulus to further clinical investigations* and study

Card ac Arrhythmias The Modern Electrophysiological Approach Edited by D M Krikler and J F Goodwin London 19 5 W B Saunders Company 264 pages

Many new books have been appearing devoted to cardiac arrhythmias This is probably prompted by the coronary-care unit (CCU) and extensive monitoring of patients as well as to the arbitrary dosage of digoxin and kaliuretic diuretics used so extensively today Each book has its virtues This one is particularly useful because it is lucid simple and nicely illustrated The various contributors have written their chapters for the clinician and trainee in cardiology Furthermore the arrhythmias discussed are the common ones which so frequently plague the physician The rare and extremely *controversial disturbances in the heart beat are barely* mentioned or not discussed at all since not only are most of them rare but their mechanisms are not understood or have several possible explanatory mechanisms This book is simple practical and useful to physicians who treat cardiac disease As in any book, any reviewer can find differences of opinion but as a whole this is a good relatively concise discussion of cardiac arrhythmias As is the practice these days *the fundamental and original work of the past is either unknown to the* respective contributors or has been ignored by them Most of the subject of cardiac arrhythmias has been known for 50 or more years The respective bibliographies *do not reflect this Therefore the historical aspects of the respective chapters are* weak

Books received

Erythropoies s Edited by Kiku Nakao James W Fisher Fumimaro Takakama Baltimore Md 19 6 University Park Press 509 pp Price $33 50

The P nc ples and Pract ces of Med c ne 19th Fdition Edited by A M Harvey Richard J Johns *Albert H Owens Jr and* Richard S Ross New York N Y 19 6 Appleton Century Crofts, 1813 pp

Kl matog af a Slovenska By Prof M U Dr Juraj Hensel and R N Dr Stefan Petrovic Bratislava *Czechoslovakia* 19 6 Vydavatelstvo Osveta 419 pages

Forecast ng in Cardiology By E Stoupel Jerusalem Israel 19 6 Israel Universities *Press* 129 pages

Evaluat ons of Drug Interactions 2nd edit on American Pharmaceutical Association Washington D C 1976 American Pharmaceutical Association 590 pages *Price* $12 50

good ingredients and careful preparation are all that is needed? Since Monosodium Glutamate poses a health hazard shouldn t the Food and Drug Administration look into its use by the food processors?

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REFERENCES

1 Alston R M Chinese Restaurant Syndrome N Er J Med **294** 225 1976
2 Kenney R A and Tidball C S Human suscepti to oral monosodium L glutamate Am J Cl N **25** 140 1972

American Heart Journal

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ditorial

hrombolytic therapy

rls

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ithin the past decade a large volume of data has been accumulated by means of clinical trials designed to test the effectiveness of thrombolytic agents. Within the same period of time information on the processes of thrombogenesis and fibrinolysis and the extent of their importance in disease have also grown dramatically. We are now in a position to look at the data accumulated on this type of therapy and to consider its realistic value in current medical practice as well as the role it might play in other untested situations.

Although the thrombogenic process involves both platelet function and fibrin formation, the relative role of each in venous or arterial disease is not clear. Further, since dissolution of fibrin (fibrinolysis) is theoretically important in the resolution of both arterial and venous thrombi, therapeutic agents which stimulate fibrinolysis may function as thrombolytic agents. The agents available at this time are proteins which convert plasminogen to plasmin, specifically urokinase derived directly from human urine or from cultured kidney cells, and streptokinase derived from streptococcal species. Controlled clinical studies have been conducted on pulmonary embolism, myocardial infarction, and to a lesser extent on deep vein thrombosis. Less well controlled studies have been done in retinal vascular occlusion and a variety of other disorders. These data have been reviewed recently and are summarized briefly below.[1]

Pulmonary embolism

A number of small trials *completed in the* 1960's suggested that pulmonary emboli were more rapidly resolved when a thrombolytic agent was employed. Two controlled clinical *trials* conducted by the National Heart and Lung Institute—urokinase pulmonary trial (UPET) and *urokinase-streptokinase* pulmonary embolism *trial* (USPET)—compared these therapies with *standard anticoagulant* therapy on 327 patients.[2] The endpoints were angiography, *ventilation-perfusion* lung scans, and selective catheterization. *All* these parameters suggested more rapid *resolution* of pulmonary emboli in those patients treated *with* thrombolytic agents although there were no differences in mortality rates between the various treatment groups. Streptokinase and urokinase were equally effective with regard to resolution rate, as were 12 hour and 24 hour periods of administration. The differences in resolution rate were most marked in hypotensive patients.

Myocardial infarction

Numerous studies have been done to determine the effectiveness of thrombolytic agents in myocardial infarction. Most of these have been aimed at measurement of mortality rate in the patient with an acute infarct, and early studies showed significant mortality rate decreases with thrombolytic *treatment*. These studies employed general ward hospitalization of patients and this

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Continuing Medical Education Institute seminar

On April 23 through 30 1977 The Continuing Medical Education Institute will present a seminar entitled The Changing Seasons of Life The Physician s Role Sponsoring agencies are the Charles R Drew Postgraduate Medical School Office of Continuing Education in collaboration with the University of Cincinnati College of Medicine Office of Continuing Medical Education and N H Chamberlain & Associates Inc The seminar will be held in Washington D C and it has AMA accreditation For further information please write N H Chamberlain & Associates Inc 2100 19th St N W #601 Washington D C 20009

Seminar on cardiac arrhythmias

A three day intensive course entitled The electrophysiological basis for diagnosis and treatment of cardiac arrhythmias is being cosponsored by the University of Illinois College of Medicine the American Heart Association and the Chicago Heart Association The seminar will be held on October 26 through 28 1977 at the Drake Hotel in Chicago The program will feature an array of guest speakers of international renown including Dr Hein Wellens of the Netherland The course offers 22 hours of Category I credit toward the Physicians Recognition Award of the AMA Course director is Dr Kenneth Rosen

Emphasis of course content will be upon updating the information derived from current techniques used in the diagnosis and treatment of cardiac arrhythmias Mechanisms of arrhythmias will be explored in depth and rational therapy based upon these mechanisms will be discussed For further details and registration information please contact University of Illinois at the Medical Center Office of Continuing Education Services 1853 W Polk St Room 144 Chicago Ill 60612 or telephone (312) 996 8025

International Society for Heart Research meeting

The Annual Meeting of the American Section of the International Society for Heart Research will be held on May 13 and 14 1977 in Pasadena California For further information regarding this meeting please write Dr Richard B... Professor of Medicine University of Southern Cali... Huntington Memorial Hospital 100 Congress St Pasad... Calif U S A 91105

Postgraduate course on MI and angina

The Second International Postgraduate Course on Myocardial Infarction and Angina Pectoris will be held on M... through 26 1977 in Davos Switzerland at the Davos Ce... tion Center Program directors are Dr Paul Lichtlen and Dr Bertram Pitt Course registration fees are $1?5 (U S funds) regular registration and $125 (U S funds) for fellows and residents in training

This five day continuing medical education course is presented by the Cardiology Departments of The J... Hopkins University School of Medicine and the Medical University of Hannover The course is open to all phy... and surgeons with an interest in myocardial infarction and angina pectoris It will review current concepts regarding management of patients with angina pectoris and MI Spe... symposia panel discussions and workshops have been arranged to allow an exchange of ideas and approach between American and European participants All lec... will be in English The course is approved for 30 Cate... credit hours for AMA recognition For further information please write Program Coordinator The Johns Ho... Medical Institutions Turner Auditorium Room 1? Rutland Ave Baltimore Md 21205

Advances in Cardiology symposium

A three day symposium entitled Advances in Cardiology will be held at the Palm Springs Riviera Hotel Palm Spr... California on March 14 through 16 1977 The symposium will be sponsored by the Foundation for Cardiovascular Research and by the Hospital of the Good Samaritan Topics will cover the pathogenesis diagnosis treatment and rehabilitation of myocardial infarction as well as case presentation and clinical correlations

Please direct all inquiries to the Foundation for Cardiovascular Research 10 Congress St Suite 203 Pasadena Calif 91105

ct size may provide a pathway to more tive detection of thrombolytic effect Pend uch data thrombolytic agents do not have a role in the patient with an acute infarct

eep vein thrombosis is a common and poten y life threatening disease The data in hand onstrate more rapid resolution with thrombo treatment and suggest that this prevents ve damage which causes the post phlebitic drome Since no effect on incidence of pulmo y embolism has been presented the physician st base his decision on a balance between reased probability of chronic venous insuffi ncy and the increased risk of thrombolytic over ventional anticoagulant therapy More data is eded to assist the clinician in this situation kewise the information available for a host of ner disorders is little more than anecdotal and es not permit reasoned decisions

In the past several years our knowledge of asminogen and fibrinogen chemistry has reased dramatically This has allowed ac mulation of data relevant to the interaction of e fibrinolytic system and other triggered nzyme systems (the kinin system and comple ent) At the present time the interactions ithin these systems are incompletely understood nd a full appreciation of these reactions and heir various inhibitors and feedbacks does not seem to be within easy reach Although there is vidence that streptokinase and urokinase pro duce lysis of fibrin *in vivo* the advantages in a number of clinical states are not equally clear urther clinical application of such fibrinolytic nhancement may need to await the under tanding of interaction between the various trig gered enzyme systems alluded to above At such time manipulation of these systems with agents other than the protein fibrinolysins may be possible and desirable

With the data now in hand the clinical investi gator has available to him in the thrombolytic agents a range of therapeutic properties different from any other agents now available These must be employed with careful clinical monitoring and the appropriate laboratory controls If these agents are released for general clinical use in the near future it is unlikely that clinical data beyond that summarized above will be available Thus in order to decide on the risk versus the benefit for any particular patient the physician will need to consider many factors before using these unique and potent agents

REFERENCES

1 *Fratantoni J C Ness P and Simon T L* Thrombolytic therapy Current status N Engl J Med **293** 1073 1975

2 A National Cooperative Study The urokinase-pulmonary embolism trial, Circulation **47** (Suppl 2) 1 108 1973

3 A National Cooperative Study Urokinase-streptokinase pulmonary embolism trial phase 2 results J A M A **229** 1606 1974

4 European Working Party Streptokinase in recent myocardial infarction A controlled multicenter trial Br med J 3 325 1971

5 Duckert F European Urokinase Trial in Myocardial Infarction Proceedings of the Third Congress of the International Society of Thrombosis and Hemostasis Washington D C August 22 26 1972 p 418

6 Kakkar V V Treatment of deep vein thrombosis A trial of heparin streptokinase and Arvin Bull Swiss Acad Med Sci **29** 253 1973

7 Kwaan N C Fetkenhour C L Dobbie J G and Grumet G N Thrombolytic and anticoagulant therapy of occlusive retinal vascular disease *Circulation* **50** (Suppl 3) 302 1974

8 Wessler S Kleiger R E Cornfield J and Teitelbaum S L Coumarin therapy in acute myocardial infarction *A Hobson s choice* Arch Intern Med **134** 74 1974

may have led to difficulty in interpretation of data For example, the European Working Party study initially found a control mortality rate of 26 3 per cent which was significantly higher than the streptokinase treated mortality rate of 18 5 per cent[4] When a second European study was done using a coronary care unit the control mortality was 13 9 per cent, which was not significantly different from the streptokinase mortality of 17 per cent[5] Later studies continue to confirm the impression that thrombolytic agents do not alter the mortality rate in acute myocardial infarction

Deep vein thrombosis

Most studies of this problem have demonstrated angiographic resolution of the thrombus that is more rapid when thrombolytic therapy is employed Prelabeling of thrombi with radioisotopically labeled fibrinogen and measurement of the rate of resolution also confirms these results A study by Kakkar suggests that incidence of the post phlebitic syndrome is decreased as a result of this treatment No change in frequency of pulmonary embolism has been documented

Ophthalmologic uses

Most studies have concentrated on retinal arterial or retinal venous thrombi These studies have not been carefully controlled for duration of disease or for endpoints The recent results of Kwaan and associates are encouraging but a rigidly controlled study comparing thrombolytic treatment with anticoagulated and non anticoagulated controls has not been completed

Peripheral arterial thrombosis

Data on the efficacy in peripheral arterial occlusion, acute or chronic do not provide a clear conclusion Chronic lesions have generally not responded favorably and in acute lesions controlled studies are not satisfactory and a surgical approach is often preferred

Other disorders

Evidence has accumulated to document the importance of fibrin deposition in such diseases as glomerulonephritis and vasculitis Thrombolytic agents have been employed and anecdotal information is available in the hemolytic uremic syndrome and experimental renal transplantation, among others The application of these agents to such situations is intriguing and furth data are awaited

Complications of therapy

The production of a fibrinolytic state cau interference with normal hemostasis This analogous to but more severe than the interfe ence caused by classical anticoagulant therap with warfarin or heparin Patients chosen for th NHLI trials were rigidly screened In addition t the usual contraindications to anticoagula therapy the following criteria resulted in exclu sion recent surgical procedures (within ten day of treatment) including liver biopsy renal biop thoracentesis or lumbar puncture cerebrova cular accident or intracranial operation within two months and evidence of a lesion known or suspected to be associated with intracranial hemorrhage Approximately one half the patient in the NHLI trials experienced some type of bleeding but this was primarily from puncture sites

Discussion

If we consider the pulmonary embolism and myocardial infarction trials, the results are n encouraging In these high mortality disorde the *death rate was not affected* by treatmen Pulmonary embolism produces angiographic and hemodynamic changes which permit serial mea surement of resolution From the study group available we can conclude that thrombolytic *agents hasten resolution of massive* pulmonar emboli but do not decrease the mortality rate In patients suffering massive pulmonary embolism with pre existent pulmonary or cardiac insuffi ciency where more rapid resolution of the embolus might be *beneficial* thrombolytic thera py is an alternative to surgical embolectomy Further observation will be needed to clarify the question in that group of patients

Myocardial infarction studies provide even less cause for optimism When mortality rate i used as the endpoint thrombolytic therapy shows no effect in well controlled studies The pitfalls inherent in use of the mortality rate endpoint are well recognized the treatment being tested may affect only one of the many factors causing death thus altering the sample size required for signifi cance (This was a problem with anticoagulant studies in myocardial infarction[8]) The new techniques for determination of myocardial

er Cardiac output was computed on line the thermal and dye dilution concentration s by the gamma variate technique[9] on a x Data Systems Sigma 3 computer asurement were made of cardiac index (CI) rate systemic and pulmonary artery pres and where possible the pulmonary wedge ure In instances where the pulmonary e pressure could not be obtained the ionary artery diastolic pressure was used as a titute for it From these data the stroke index stroke work index (SWI) total systemic tance and the pulmonary vascular resi tance computed All hemodynamic data reported his study during IABC were recorded while patient was being assisted with every beat

or the purpose of analyzing the hemodynamic nges occurring over time sets of data were sen from each patient that were obtained ore the initiation of counterpulsation and as e as possible to 12 24 48 72 and 96 hours of rapy The actual mean times of data acquisi n for each of these periods were respectively 0 6 hours prior to and 9 ± 0 08 hours ± 0 9 hours 44 ± 2 5 hours 67 ± 3 3 hours 1 96 ± 4 2 hours after the initiation of ther y

Termination of counterpulsation was at npted in all but one patient between 29 and 66 urs of therapy and consisted of a stepwise duction in the frequency of balloon assist The tio of assisted to spontaneous beats was ngressively reduced from 1 1 to 1 2 to 1 4 to 8 as the patient s clinical condition permitted ounterpulsation was continued for 2 to 4 hours each stage of the withdrawal process Balloon pendence was determined by *persistence of* ute pulmonary edema recurrent cardiogenic iock uncontrollable chest pain or a combina on of these findings during balloon withdrawal ll hemodynamic results are expressed as the ean ± standard error of the mean Comparison the magnitude of hemodynamic changes in lloon dependent and balloon independent pa nts was performed with the unpaired t test

esults

A description of the patient population is pre nted in Table I Four patients showed no versal of the shock syndrome and died within e first 30 hours of counterpulsation Twelve tients showed reversal of the shock syndrome

Table I Study population

Subject	Age	Site of infarct	Outcome
Shock not reversed			
W K	5?	Diaphragmatic	Died during IABC
R B	53	Anteroseptal	Died during IABC
L L	61	Anteroseptal	Died during IABC
N F	60	Anterolateral	Died during IABC
Shock reversed			
Balloon dependent			
E G	65	Diaphragmatic	Died during prolon ged IABC
H D	51	Anterolateral	Intraoperative death
D L	61	Anterolateral	Intraoperative death
C G	63	Anterior	Hospital death fol lowing IABC withdrawal
G F	41	Diaphragmatic	Hospital survivor following surgery
F R	5?	Diaphragmatic	Hospital survivor
Ballon independent			
W K	51	Diaphragmatic	Hospital survivor
E M	64	Anterolateral	Hospital survivor
M K	4?	Anterolateral	Hospital survivor
K B	?8	Anterolateral	Hospital death
W B	43	Anterolateral	Hospital death
A Y	6?	Diaphragmatic	Died with acute pulmonary embolus

manifested clinically as an increase in urine flow improvement in mentation and improved blood flow to the extremities Five patients were found to be balloon independent when balloon with drawal was attempted between 29 and 66 hours of therapy Of these five patients three were discharged to home and two died in the hospital One died of rupture of the left ventricular free wall and the other as a result of sepsis One patient whose shock was reversed by counterpul sation died of acute pulmonary embolism before balloon withdrawal could be attempted The remaining six patients were found to be balloon dependent One of these six patients received continued counterpulsation and died after 136 hours of IABC Five balloon dependent patients underwent selective coronary arteriography and ventriculography Three of the five patients were found to have surgically remediable coronary arterial disease Two patients died intraopera tively and the third survived and left the hospital The remaining two patients who underwent angiographic study had no surgically remediable

Clinical communications

The hemodynamic response to intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction

Dennis A Ehrich, M D
Theodore L Biddle, M D
Marvin W Kronenberg M D
Paul N Yu, M D
Rochester N Y

Cardiogenic shock is a serious *complication* of acute myocardial infarction and, *without* inter vention carries a mortality *rate of almost* 100 per cent Intra aortic *balloon counterpulsation* (IABC) when applied in *cardiogenic shock* complicating acute myocardial *infarction* has been demonstrated *to reverse the clinical shock* syndrome and partially *rectify the* hemodynamic abnormalities in a number *of patients* [1-5] The mortality rate *of the shock* syndrome after IABC application was reduced to 70 to 84 per cent *when* used alone [3-5] and 55 to 60 per *cent* when combined with a surgical procedure [2,6]

The present study was *undertaken* to define the serial hemodynamic changes during *the first 96* hours of IABC and their *possible* relation to outcome

Materials and methods

The study population consisted of 16 *patients* with cardiogenic shock admitted to the Myocar dial Infarction Research Unit (MIRU) at the University of Rochester Medical Center *between* Oct 5 1972, and Oct 5 1974 *Each of the* patients studied met the following *criteria* (1) evidence of acute myocardial infarction as determined from the clinical history serial electrocardiograms *and* serum enzyme studies, (2) a systemic arterial systolic blood pressure less than 90 mm Hg, cold and clammy skin, impaired mentation and oliguria (20 c c per hour urine flow or less) and (3) inadequate response to pressor agents.

All patients underwent right heart catheterization with a flow directed thermistor tip catheter [7] An 18 gauge Longdwell cannula was inserted in a brachial artery Twelve patients required intubation and controlled ventilation for profound hypoxemia

Following insertion of a 40 c c balloon catheter via a femoral arteriotomy with a sidearm graft IABC was established with the AVCO intra aortic balloon pump All patients were anticoagulated with heparin sulfate and received an infusion of 10 c c per hour of low molecular weight dextran *during the time* the balloon was in place

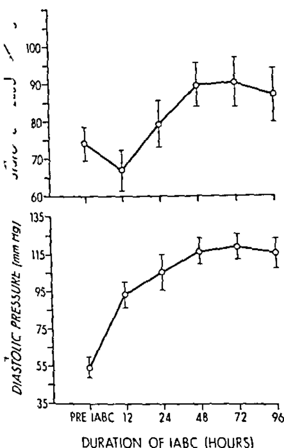
Intravascular pressures were recorded with Statham SP37 strain gauge transducers and a direct writing Clevite Brush recorder The zero reference level was taken as 5 cm below the sternal angle Cardiac output was measured by *the thermal dilution* technique with a 10 c c *bolus of* 0° C 5 per cent dextrose in water as the indicator or by the dye dilution technique with indocyanine green injected into the pulmonary artery All cardiac output measurements were *made* in triplicate In the case of indocyanine green injection blood was withdrawn from the brachial artery by a Harvard withdrawal infusion pump and returned to the patient under aseptic conditions Measurements of optical density of the dye were made with a Gilford cuvette densi

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[Fig.] 3 Systemic artery systolic and peak diastolic pressures [during] intra aortic balloon counterpulsation in 16 patients [over 96] hours of treatment

[u]ndergo a trial of balloon withdrawal were [s]ubdivided into two groups (1) balloon independent and (2) balloon dependent Comparison was [m]ade of the relative magnitude of the hemodynamic response to counterpulsation in each of the subgroups (Fig 4) During the first 12 hours of IABC the magnitude of increase in cardiac index [s]troke index and stroke work index was quite [s]imilar in both balloon independent and balloon [de]pendent groups The balloon independent [g]roup experienced a 100 per cent increase in [sys]temic artery diastolic pressure as opposed to a 3[?] per cent increase observed in balloon dependent patients (63 ± 3 vs 27 ± 3 mm Hg increase $p < 0.0025$)

However between 12 and 24 hours after IABC the significant augmentation of cardiac index stroke index and stroke work index noted for the total group appeared to reside almost exclusively in the patients found ultimately to be balloon independent For cardiac index there was a 47 per cent increase in the balloon independent group vs a 3 per cent increase in balloon dependent patients (0.9 ± 0.2 vs 0.06 ± 0.09 L/min/M increase $p < 0.005$) For stroke index there was a 49 per cent increase in the balloon independent group vs a 0.3 per cent increase in the balloon dependent patients (10 ± 0.9 vs 0.06 ± 0.6 ml/

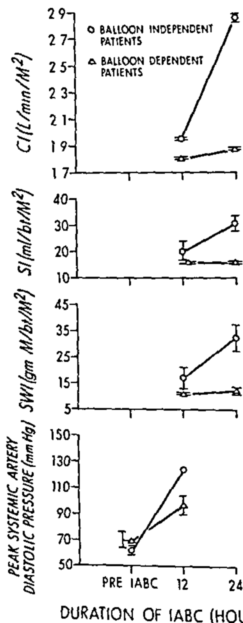


Fig 4 Comparison of the response of cardiac index (CI) stroke index (SI) stroke work index (SWI) and peak systemic artery diastolic pressure to intra aortic balloon counterpulsation in balloon independent (circles) and balloon-dependent (triangles) patients Note the significantly greater increases in these parameters in balloon independent as compared with balloon-dependent patients

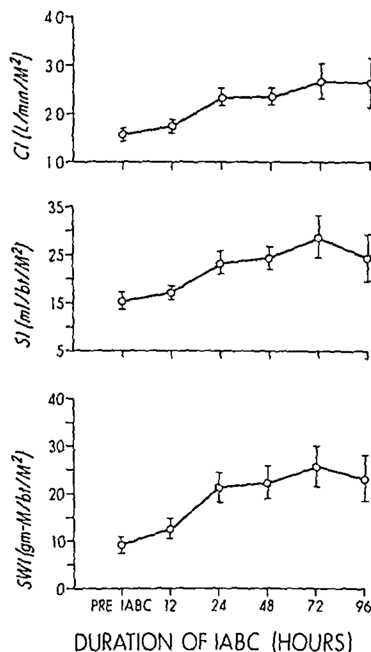


Fig 1 The response of cardiac index (CI) stroke index (SI) and stroke work index (SWI) to intra aortic balloon counterpulsation in 16 patients over 96 hours of treatment In this and subsequent figures SWI in Gm M /beat/M is depicted as SWI (Gm M /bt M)

lesions They received continued counterpulsation with successful withdrawal from the balloon after approximately 200 hours of IABC One survived and left the hospital and the other died while on hemodialysis 3 days after withdrawal from IABC The over all hospital survival rate was 31 per cent (5 of 16)

The results of serial hemodynamic measurements for the total patient group are presented in Figs 1 to 3 Statistical analysis indicated that there was significant improvement within the first 12 hours of IABC therapy in cardiac index (1 5 ± 0 2 to 1 9 ± 0 2 L /min /M , p < 0 0001)

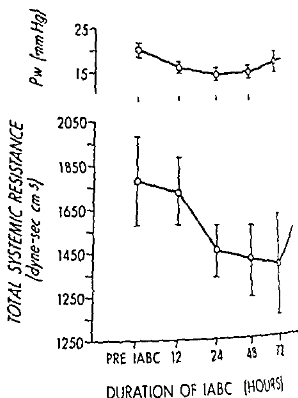


Fig 2 The pulmonary wedge pressure (Pw) and systemic resistance during intra aortic balloon counterpulsation over 96 hours of treatment Note the late increase … parameters

stroke index (15 ± 2 to 20 ± 2 ml /beat … p < 0 002) and stroke work index (10 ± 2 … 15 ± 3 2 Gm M /beat/M p < 0 03) The three hemodynamic parameters improved e… further between 12 and 24 hours (CI 1 8 ± 0 1 … 2 3 ± 0 2 L /min /M p < 0 02 SI 17 ± … 23 ± 3 ml /beat/M p < 0 02 and SWI 13 ± 2 0 to 20 ± 3 6 Gm M /beat/M , p < 0 … The pulmonary wedge pressure decreased in the first 24 hours of therapy (20 ± 2 to 15 ± 2 mm Hg p < 0 04) The total systemic resistance fell … the first 24 hours (2 055 ± 206 to 1 471 ± … dynes sec cm p < 0 01) with further reduction between 24 and 48 hours (1 583 ± 140 to 1 413 ± 158 dynes sec cm p < 0 03) The systemic artery peak diastolic pressure (assisted diastolic pressure) increased significantly in the first 12 hours of therapy (56 ± 5 to 98 ± 9 mm Hg p < 0 001) and the systolic pressure was found to increase between 12 and 24 hours (69 ± 6 to 81 ± 7 mm Hg p < 0 025) Counterpulsation produced no significant changes in heart rate mean pulmonary artery pressure mean systemic artery pressure or pulmonary vascular resistance

The 11 patients whose shock was reversed by counterpulsation and who also survived to

-ı LVFP ın our patients ıs somewhat lower and ventricular function curves ın our patients ɾm 24 through 72 hours after counterpulsation positioned further upward and to the left than ›se reported by Dilley and associates

When the hemodynamic data obtained ın the t 12 to 24 hours from the balloon independent tients are compared with those from the lloon dependent patients ıt becomes obvious at ın the former group a significantly greater rease ın systemic artery peak diastolic pressure curs ın the first 12 hours of IABC and a nificantly greater increase ın cardiac index roke index and stroke work index ıs noted tween 12 and 24 hours of IABC when compared ıth the latter patients These observations must considered preliminary ın view of the small ımple sizes involved and should be tested ın ırger populations If these findings are con rmed they may allow identification of balloon ependent patients within the first 24 hours of ounterpulsation

The hospital survival ın our series ın 31 per cent ıth IABC alone and 33 per cent with IABC and oronary revascularization Our results are com ıarable to those reported by other authors It hould be pointed out however that combined ABC and surgery may indeed improve hospital urvival beyond that which can be attained with IABC alone Thus early identification of balloon-dependent patients not only avoids hemodynamic deterioration with prolonged bal loon assistance but also facilitates earlier initia tion of coronary angiogram and possible coronary revascularization than have been customarily done ın the past

Summary

Sixteen patients with cardiogenic shock compli cating acute myocardial infarction underwent serial hemodynamic studies during intra aortic balloon counterpulsation (IABC) at an assist frequency of 1 1 Significant increase was noted during the first 12 hours of IABC ın the systemic artery peak diastolic pressure (assisted) cardiac index stroke index and stroke work index During the second 12 hours further significant improvement was noted ın the latter three parameters and ın addition the systemic artery systolic pressure increased significantly The pulmonary wedge pressure fell as did the total systemic resistance (TSR) during the first 24 hours of IABC Patients found to be balloon independent after reduction ın balloon assist frequency demonstrated significantly greater increase ın systemic artery peak diastolic pressure during the first 12 hours of IABC than did those patients found to be balloon dependent Likewise the improvement noted ın CI SI and SWI during the second 12 hours of IABC was of greater magnitude ın balloon independent than ın bal loon dependent patients The data suggest late hemodynamic deterioration after 48 hours of IABC

It ıs concluded that IABC ıs effective ın improving the deranged hemodynamics of car diogenic shock Maximum response ıs noted between 24 and 48 hours

It ıs suggested that patients who are balloon independent may be distinguished from those who are balloon dependent by the hemodynamic response within the first 24 hours of IABC

REFERENCES

1 Mueller H Ayres S M Conklin E F, et al. The effects of intra aortic counterpulsation on cardiac performance and metabolism ın shock associated with acute myocardial infarction J Clin Invest 50 1885 1971

2. Dunkman W B., Leinbach R C., Buckley M J., et al Clinical and hemodynamic results of intra aortic balloon pumping and surgery for cardiogenic shock Circulation 46 465 19 2

3 Scheidt S S Wilner G Mueller H et al. Intra aortic balloon counterpulsation ın cardiogenic shock Report of a cooperative clinical trial N Engl J Med 288 979 1973

4 Dilley R B Ross J Jr and Bernstein E F Serial hemodynamics during intra aortic balloon counterpulsa tion for cardiogenic shock Circulation 47 48(Suppl III) III 99 1973

5 Kantrowitz A Krakauer J S Rosenbaum A et al. Phase shift balloon pumping ın medically refractory cardiogenic shock. Results ın 27 patients Arch Surg 99 739 1969

6 Miller M G Hedley White J Weintraub R M et al. Surgery for cardiogenic shock Lancet 2 1342 1974

7 Forrester J S Ganz W Diamond G et al. Thermo dilution cardiac output determination with a single flow directed catheter AM HEART J 83 306 1972

8 Kantrowitz A Phillips S J Butner A N et al. Technique of femoral artery cannulation for phase shift balloon pumping. J Thorac. Cardiovasc Surg 56 219 1968

9 Starmer C H and Clark D O Computer computa tions of cardiac output using the gamma function J Appl Physiol. 28 219 1970

10 Soroff H S., Levine H J., Sachs B F et al. Assisted circulation II Effects of counterpulsation on left ventricular oxygen consumption and hemodynamics Circulation 27 722 1963

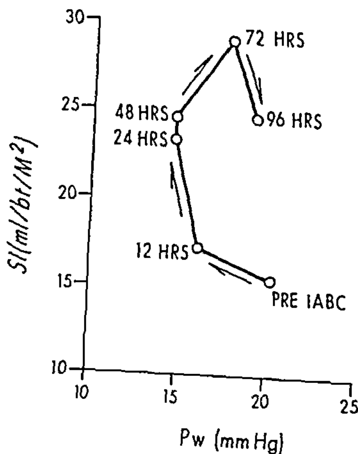


Fig 5 The relationship of stroke index (SI) and pulmonary wedge pressure (Pw) during 96 hours of intra aortic balloon counterpulsation Note the apparent deterioration of left ventricular function after 48 hours of therapy

beat/M , $p < 0.0005$) For stroke work index there was a 90 per cent increase in the balloon independent group vs a 7 per cent increase in balloon dependent patients (15 ± 4 vs 0.8 ± 1 Gm M /beat/M $p < 0.0025$) After 48 hours the pulmonary wedge pressure tended to rise After 72 hours stroke index stroke work index and systemic artery pressure were reduced whereas there was an increase in total systemic resistance

Discussion

The data reported in this study demonstrate a salutary effect of IABC on hemodynamics which is evident within 12 hours after the initiation of counterpulsation The improvement is characterized by an appreciable reduction in the pulmonary wedge or pulmonary artery diastolic pressure both presumably reflecting left ventricular filling pressure (LVFP) associated with significant increase in the cardiac index stroke index and stroke work index The total systemic resistance falls over the first 24 hours and continues to fall up to 48 hours of counterpulsation It would appear from our data that hemodyn[...] improvement is maximal at 24 hours of [...] therapy After 48 hours the trend of the hem[...]namic data indicates an increase in pulmo[...] wedge pressure and after 72 hours there is [...] reduction in stroke index and stroke work i[...] accompanied by an increase in total sy[...] resistance Similar observations of second[...] hemodynamic deterioration on IABC have be[...] reported by others

It is of interest that the hemodynamic d[...] from the total patient group presented in Fig [...] 3 indicate an initial reduction in systemic ar[...] systolic pressure within the first 12 hours of therapy Although the magnitude of this ch[...] is not statistically significant, it is nonethele[ss] the direction that one would anticipate w[...] effective phase shift counterpulsation Likew[ise] the reduction in stroke index and stroke w[ork] index after 72 hours, the increase in pulmonary wedge pressure and total systemic resistance af[ter] 48 and 72 hours respectively, and the reductio[n in] systemic artery systolic as well as peak dia[stolic] pressures after 96 hours reflect potentially u[nfa]vorable trends as the IABP continues beyond [...] hours

From the standpoint of the Frank Starl[ing] relationship as depicted in Fig 5 ventric[ular] function appears to improve significantly over the first 24 hours Between 24 and 48 hours increase[d] stroke volume is maintained at the same LVF[P] implying slight improvement in ventricular fun[c]tion From 48 hours to 72 hours stroke index is augmented at the expense of an increase in LVFP This change could be explained on the basis of a shift to the right and upward along the same function curve as at 48 hours However since all patients were maintained in slightly negative fluid balance during counterpulsation this change probably reflects a shift to an adjacent but slightly more depressed ventricular function curve Between 72 and 96 hours ventricular function is clearly depressed with a shift of the curve downward and to the right Dilley and associates have described a sequence of changes in ventricular function similar to our own in direction but differing in magnitude and time course This difference may be due to a difference in the initial amount of ventricular dysfunction in the two patient populations or to the fact that our patients did not uniformly undergo a trial of plasma volume expansion The precounterpulsa

LVFP in our patients is somewhat lower and ventricular function curves in our patients 24 through 72 hours after counterpulsation positioned further upward and to the left than se reported by Dilley and associates.[4]

When the hemodynamic data obtained in the 12 to 24 hours from the balloon independent ients are compared with those from the loon dependent patients, it becomes obvious t in the former group a significantly greater rease in systemic artery peak diastolic pressure urs in the first 12 hours of IABC and a nificantly greater increase in cardiac index, oke index, and stroke work index is noted tween 12 and 24 hours of IABC when compared th the latter patients. These observations must considered preliminary in view of the small mple sizes involved and should be tested in rger populations. If these findings are con rmed they may allow identification of balloon pendent patients within the first 24 hours of unterpulsation.

The hospital survival in our series in 31 per cent ith IABC alone and 33 per cent with IABC and oronary revascularization. Our results are com arable to those reported by other authors.[1] It hould be pointed out, however, that combined ABC and surgery may indeed improve hospital urvival beyond that which can be attained with ABC alone. Thus early identification of balloon dependent patients not only avoids hemodynamic deterioration with prolonged bal loon assistance but also facilitates earlier initia tion of coronary angiogram and possible coronary revascularization than have been customarily done in the past.

Summary

Sixteen patients with cardiogenic shock compli cating acute myocardial infarction underwent serial hemodynamic studies during intra aortic balloon counterpulsation (IABC) at an assist frequency of 1:1. Significant increase was noted during the first 12 hours of IABC in the systemic artery peak diastolic pressure (assisted), cardiac index, stroke index, and stroke work index. During the second 12 hours further significant improvement was noted in the latter three parameters and in addition the systemic artery systolic pressure increased significantly. The pulmonary wedge pressure fell as did the total systemic resistance (TSR) during the first 24 hours of IABC. Patients found to be balloon independent after reduction in balloon assist frequency demonstrated significantly greater increase in systemic artery peak diastolic pressure during the first 12 hours of IABC than did those patients found to be balloon dependent. Likewise the improvement noted in CI, SI, and SWI during the second 12 hours of IABC was of greater magnitude in balloon independent than in bal loon dependent patients. The data suggest late hemodynamic deterioration after 48 hours of IABC.

It is concluded that IABC is effective in improving the deranged hemodynamics of car diogenic shock. Maximum response is noted between 24 and 48 hours.

It is suggested that patients who are balloon independent may be distinguished from those who are balloon dependent by the hemodynamic response within the first 24 hours of IABC.

REFERENCES

1. Mueller H, Ayres S M, Conklin F F, et al: The effects of intra aortic counterpulsation on cardiac performance and metabolism in shock associated with acute myocardial infarction. J Clin Invest 50:1885, 1971.
2. Dunkman W B, Leinbach R C, Buckley M J, et al: Clinical and hemodynamic results of intra aortic balloon pumping and surgery for cardiogenic shock. Circulation 46:465, 1972.
3. Scheidt S S, Wilner G, Mueller H, et al: Intra aortic balloon counterpulsation in cardiogenic shock. Report of a cooperative clinical trial. N Engl J Med 288:979, 1973.
4. Dilley R B, Ross J Jr, and Bernstein E F: Serial hemodynamics during intra aortic balloon counterpulsation for cardiogenic shock. Circulation 47, 48(Suppl III):III 99, 1973.
5. Kantrowitz A, Krakauer J S, Rosenbaum A, et al: Phase shift balloon pumping in medically refractory cardiogenic shock. Results in 27 patients. Arch Surg 99:739, 1969.
6. Miller M G, Hedley White J, Weintraub R M, et al: Surgery for cardiogenic shock. Lancet 2:1342, 1974.
7. Forrester J S, Ganz W, Diamond G, et al: Thermodilution cardiac output determination with a single flow directed catheter. Am Heart J 83:306, 1972.
8. Kantrowitz A, Phillips S J, Butner A N, et al: Technique of femoral artery cannulation for phase shift balloon pumping. J Thorac Cardiovasc Surg 56:219, 1968.
9. Starmer C H, and Clark D O: Computer computations of cardiac output using the gamma function. J Appl Physiol 28:219, 1970.
10. Soroff H S, Levine H J, Sachs B F, et al: Assisted circulation. II. Effects of counterpulsation on left ventricular oxygen consumption and hemodynamics. Circulation 27:722, 1963.

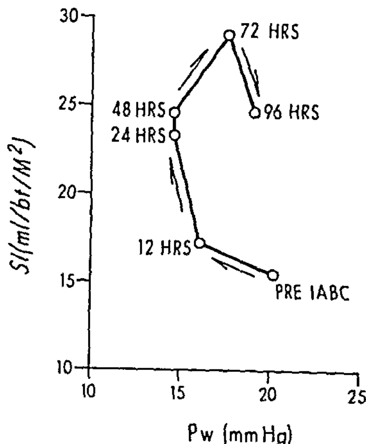


Fig 5 The *relationship* of stroke index (SI) and pulmonary wedge pressure (Pw) *during 96 hours* of intra aortic balloon counterpulsation Note *the apparent* deterioration of left ventricular function after 48 hours of *therapy*

beat/M p < 0 0005) For stroke work index *there* was a *90* per cent increase in the balloon *independent* group vs a 7 per cent increase *in* balloon dependent patients (15 ± 4 vs 0 8 ± 1 Gm M /beat/M p < 0 0025) After 48 hours the pulmonary wedge pressure tended to rise *After 72* hours stroke index stroke work index *and* systemic artery pressure were reduced whereas there was an increase in total systemic resistance

Discussion

The data reported in this study demonstrate a salutary effect of IABC on hemodynamics which is evident within 12 hours after the initiation of counterpulsation The improvement is characterized by an appreciable reduction in the pulmonary wedge or pulmonary artery diastolic pressure both presumably reflecting left ventricular filling pressure (LVFP) associated with significant increase in the cardiac index stroke index and stroke work index The total systemic resistance falls over the first 24 hours and continues to fall up to 48 hours of counterpulsation It would appear from our data that hemod improvement is maximal at 24 hours of I therapy After 48 hours the trend of the he *namic data* indicates an increase in pulm *wedge* pressure and after 72 hours there reduction in stroke index and stroke work accompanied by an increase in total sy resistance Similar observations of second hemodynamic deterioration on IABC have b reported by others

It is of interest that the hemodynamic d *from the* total patient group presented in Fig 1 3 indicate an initial reduction in systemic art systolic pressure within the first 12 hours therapy Although the magnitude of this ch is not statistically significant, it is nonetheless the direction that one would anticipate wi effective phase shift counterpulsation [10] Likewise the reduction in stroke *index* and stroke w *index* after 72 hours the increase in pulmo wedge pressure and total systemic resistance af 48 and 72 hours respectively, and the reduction systemic artery systolic as well as peak diastolic pressures after 96 hours reflect potentially u vorable trends as the IABP continues beyo hours

From the standpoint of the Frank Starl relationship as *depicted in Fig* 5 ventric *function* appears to improve significantly over *first* 24 hours Between 24 and 48 hours increase stroke volume is maintained at the same LVF implying slight improvement in ventricular fun tion From 48 hours to 72 hours stroke index augmented at the expense of an increase in LVFP This change could be explained on the basis of a shift to the right and upward along the same function curve as at 48 hours However since all patients were maintained in slightly negative fluid balance during counterpulsation th *change* probably reflects a shift to an adjacent *but slightly* more depressed ventricular functio *curve* Between 72 and 96 hours ventricu function is clearly depressed with a shift of the curve downward and to the right Dilley and associates have described a sequence of changes in ventricular function similar to our own in direction but differing in magnitude and time course This difference may be due to a difference in the initial amount of ventricular dysfunction in the two patient *populations or to the fact* that our patients did not *uniformly undergo* a trial of plasma volume expansion The precounterpul

le I Summary of clinical and pathologic data in 24 patients in cardiogenic shock (without
hanical lesion)*

Patients No.	Age	Sex	Infarct	Interval (hr)	Duration of IABP (hr)	Vessels 75% or more obstructed			Operation	Outcome
	51	M	S	9	36	LAD (100%)	RCA (100%)	LCA	No	Died on IABP (shock not reversed)
	6	F	A old I	16	18	LAD	RCA		No	Died (leg ischaemia removal of the balloon recurrent shock)
	[illegible]	F	I	3	4	–	–	–	No	Died on IABP (ventricular fibrillation) 5 hours
	61	M	AS old I	8	64	LAD	RCA	LCA	No	Weaned from IABP Died (pneumonia) 30 days
	5[illegible]	F	S	5	60	LAD (100%)	RCA	LCA (100%)	No	Died on IABP (inoperable)
	54	M	A		34	LAD (100%)		LCA (100%)	No	Died on IABP (inoperable)
	[illegible]	M	S	31	62	LAD (100%)	RCA	LCA	No	Died on IABP (recurrent shock)
	63	M	IL	1[illegible]	[illegible]	LAD	RCA		No	Weaned from IABP alive 31 months mild heart failure
	53	M	AS old I	4	30	LM			No	Died on IABP (shock not reversed)
	66	M	A old I	1[illegible]	48	LAD	RCA (100%)		No	Weaned from IABP died (acute pulmonary edema) 30 days
	[illegible]	F	A old I	10	[illegible]	LAD (100%)	RCA	LCA	No	Died on IABP (massive ventricular infarction)
	6[illegible]	M	AS old I	14	48	LAD (100%)	RCA		Yes	Died in OR (accidentally induced aortic dissection)
13	53	M	A	1	90	LAD	RCA	LCA	Yes	Died immediately postop in shock
14	[illegible]3	M	A	5	5	LAD		LCA	Yes	Alive 18 months
15	64	M	AS	11	[illegible]4	LAD	RCA	LCA	Yes	Alive 15 months
16	[illegible]	F	S	[illegible]	34	LM	RCA (100%)	LCA (100%)	No	Died on IABP (massive ventricular infarction)
1[illegible]	[illegible]0	F	C	[illegible]4	[illegible]	LM (dissection)			No	Died on IABP (massive ventricular infarction)
[illegible]	[illegible]3	F	C	6	108	LAD (100%)	RCA (100%)	LCA	No	Died on IABP (massive ventricular infarction)
19	60	F	A	6	28	–	–	–	No	Weaned from IABP alive 1 months
20	[illegible]	F	I	[illegible]4		–	–	–	No	Weaned from IABP alive 25 months mild heart failure
[illegible]1	63	M	A old I	11		LAD (100%)	RCA (100%)		No	Died on IABP
[illegible]	[illegible]4	M	A	18	63	LAD (100%)		LCA	No	Weaned from IABP died (pulmonary embolism) 3[illegible] days
[illegible]3	[illegible]	M	S	48		LAD (100%)	RCA (100%)	LCA	No	Died on IABP (shock not reversed)
[illegible]4	[illegible]	M	A	[illegible]0	4	LAD (100%)	RCA (100%)	LCA	No	Died on IABP (shock not reversed)

*Location of infarct: A = anterior; AS = anteroseptal; AL = anterolateral; I = inferior; IL = inferolateral; S = septal (AS + I); C = circumferential. Interval = time elapsed between onset of shock and IABP. LAD = left anterior descending artery; RCA = right coronary artery; LCA = Left circumflex artery; LM = left main [illegible]

patients acidosis severe hypoxemia rhythm disturbances and hypovolemia had been either excluded as a cause of shock or corrected In all cases conventional therapy (digitalis diuretics norepinephrine) administered for at least 1 hour had failed to produce any objective improvement Pulmonary artery pressure and pulmonary artery wedge pressure were measured with a Swan Ganz

Clinical and hemodynamic results of intra-aortic balloon counterpulsation and surgery for cardiogenic shock

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Left ventricular power failure resulting in cardiogenic shock as a *complication* of acute myocardial infarction *has been shown to be* associated with an extremely *high mortality* rate. Even in the patients *in cardiogenic* shock who initially respond to conventional *medical* therapy the mortality rate is *still 80 per* cent or higher and in those who fail to *respond* chances of survival are almost nil.

Mechanical circulatory assistance and in particular intra-aortic balloon pumping (*I A B P*) has been shown to be effective *in* supporting the circulation of patients in cardiogenic shock. Although temporarily good the long *term* results of clinical *application of* I A B P have been somewhat disappointing since the survival rate was less than 20 per cent. However *the* results of combining early setting of cardiac assist and emergency surgical procedures for the *treatment* of refractory cardiogenic shock complicating myocardial infarction are very encouraging. This paper reports our experience *in treating* 42 patients with medically intractable cardiogenic shock by I A B P either alone or combined with emergency surgery in 17 cases.

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Patients

The 42 patients in this series were referred from both the Coronary Care Units of Ambroise-Pa[...] and Lariboisière Hospitals from November 19[...] to March, 1974. These patients included [...] and 16 women with a mean age of 61 ± 9 ye[...] (range 37 to 76). All of them had anamne[...] electrocardiographic and enzymatic evidence of acute myocardial infarction. Patients were di[...]vided into two groups depending on the absen[...] (Group I) or the presence (Group II) of an associated mechanical lesion (rupture of the [...] septum or of a papillary muscle of the le[...] ventricle). Group I was composed of 24 patient[...] (mean age 60 ± 9 years) (Table I). The [...] interval between onset of shock and initiation [...] I A B P was 16 hours (range 3 to 18 hours). In Group II (18 patients mean age 62 ± 8 years) the infarct was complicated by a mechanical lesion (Table II). In 14 patients the mechan[...] lesion was a septal rupture which occurred with[...] 5 days *of the* infarct in 12 cases. The *rupture* w[...] situated anteriorly in 12 cases and inferiorly i[...] two cases. In the four remaining patients th[...] mechanical lesion *was a rupture of* the poster[...] papillary muscle of the left ventricle complicati[...] an inferior myocardial infarction. The me[...] interval between onset of shock and initiation [...] I A B P in this group was 11 ± 7 hours.

Recognition of the shock state was based on t[...] criteria suggested by *the United* States Myoca[...]dial *Infarction* Research Program. *In* [...]

-ble III Summary of hemodynamic data (mean ± S D) in 24 patients with cardiogenic shock thout mechanical complications*

	H R (beats/min)	Arterial pressure (mm. Hg)		P W.P (mm Hg)	C.I (L./min /M)	U O (ml./hr.)
		S	M			
Before I A B P	105	83	67	22	1.38	7
	16	19	14	5	0.39	10
During I A B P (18 ± 12 hr)	10?	80 (96)	72	16	2 00	56
	15	18 (16)	11	3	0 50	34
	NS	NS < 0 005	NS	< 0 001	< 0 001	< 0 001

*HR heart rate S systoli M Mean P W P pulmonary wedge pressure C I cardiac index U O urinary output figures in parentheses, systolic terial p essure when the balloon pump is turned off

) ensure inflation immediately following the icrotic notch and complete deflation prior to entricular systole

In addition to clinical examination ECG and hest radiograph monitoring of these patients ncluded (1) determination of serum enzymes lood cell and platelet counts (2) determination of serum and urine electrolytes and BUN twice laily (3) measurement of radial artery pressure it least every 3 to 6 hours (4) analysis of blood ases every 12 hours

All patients were under anticoagulant treatment (heparin) and recalcification time was determined twice daily Low molecular weight dextran was given intravenously at 10 c c per hour Antibiotics were not prescribed unless there was a bacteriologic proof of infection

In patients who showed improvement and whose condition was stable counterpulsation was triggered intermittently (1/3 1/4) and their hemodynamic status was reassessed after 4 to 6 hours by measurement of the cardiac index radial artery and pulmonary artery wedge pressures and blood gases If the cardiac index dropped below 2 L./min /M² if the pulmonary artery wedge pressure rose to above 20 mm Hg and if the mean radial artery pressure dropped below 50 mm Hg[10] the patient was considered balloon dependent In these cases circulatory assistance was resumed and coronary arteriography was performed If no deterioration in hemodynamic paramaters occurred intermittent counterpulsation was continued for a period of 12 hours and repeated recordings were made If these recordings failed to show any worsening the balloon was left in place for a period of 24 hours At the end of this period a complete hemodynamic study was again performed and if stabilization was documented the balloon was permanently withdrawn

Ten patients underwent coronary arteriography The latter was performed according to Sones technique in two cases and according to Bourassa s technique in eight cases Left ventriculograms were performed first in the right anterior oblique position and after a 15 minute rest period in the left anterior oblique position Films were analyzed according to the technique suggested by Sanders and associates[9] Emergency surgery was performed in 17 patients four patients had coronary artery bypass grafting and/or resection of the infarcted area in 10 patients closure of a septal defect was done with the direct suture technique[15] and three patients had mitral valve replacement

Postmortem examination was performed on 25 of the 29 patients who died

Results

Group I (24 patients) In most patients there was a marked clinical improvement after 3 to 6 hours of I A B P as evidenced by the early resumption of diuresis and the possibility of discontinuing catecholamine treatment However in four patients shock could not be reversed and these patients died while on balloon support Necropsy findings revealed massive necrosis involving over 50 per cent of the left ventricular muscle and extensive coronary disease Another patient died from intractable dysrrhythmias after 5 hours of I A B P despite a marked hemodynamic improvement Optimum clinical and hemodynamic improvement (Table III) occurred after a mean period of 18 hours of I A B P (range 1 to

Table II Summary of clinical and pathologic data in 18 patients in cardiogenic shock secondary to mechanical complications*

Patients No	Age	Sex	Infarct location	Interval (hr)	Duration of IABP (hr)	Vessels 75% or more obstructed			Rupture	Operation	Outcome
1	76	F	A	3	96	LAD	RCA		AVSD	Yes	Died 2 days postop (recurr IVSD)
2	71	F	A	6	48	LAD		LCA	AVSD	Yes	Died in OR (disruption)
3	54	M	S	21	96	LAD	RCA		AVSD	Yes	Died 5 weeks postop (sepsis, renal failure)
4	63	F	A	3	72	LAD	RCA		AVSD	Yes	Died 2 months postop (cerebrovascular accident)
5	68	M	I old A	24	226	LAD	RCA	LCA	IVSD	No	Died on IABP (extensive ventricular damage)
6	52	M	A	5	42				AVSD	Yes	Alive and well 13 months
7	53	M	A	12	24				AVSD	Yes	Alive and well 23 months
8	49	F	A	8	132				AVSD	Yes	Died in OR (disruption)
9	60	F	S	12	80				AVSD	Yes	Alive and well 2 month
10	72	F	A	6	264	LAD			AVSD	No	Died on IABP
11	69	F	S	20	216	LAD	RCA	LCA	AVSD	No	Pre existing renal failure Died on IABP
12	62	M	S	15	198	LAD	RCA	LCA	IVSD	No	Died on IABP (extensive ventricular damage)
13	68	M	S	7	108				AVSD	Yes	Alive and well 14 month
14	61	M	S	12	175				AVSD	Yes	Alive 18 months mild residual shunt
15	60	M	I	12	36		RCA		PPM	Yes	Alive and well 24 months
16	58	M	I	10	36				PPM	Yes	Alive and well 18 month
17	69	M	I	10	72				PPM	Yes	Alive and well 15 months
18	70	M	I	24	48		RCA	LCA	PPM	No	Died on IABP (ventricular fibrillation)

Infarct location = A anterior I inferior S septal (anterior and inferior) Interval time elapsed between onset of shock and IABP LAD = anterior descending artery RCA right coronary artery LCA left circumflex artery Rupture location AVSD anterior ventricular septal defect IVSD inferior septal defect PPM posterior papillary muscle

catheter and systemic arterial pressure was monitored with the aid of a catheter placed in radial artery after a cut down Cardiac output was determined by the indicator dilution method with a Waters XC 302 densitometer (Rochester Minn) In patients with ventricular septal defect, the pulmonary/systemic flow ratio was determined by oxygen saturation Pulmonary artery and systemic blood gases (Po_2 Pco_2 pH) were measured with an IL Meter and O_2 content was determined with a Lex O_2 Con (Lexington Waltham, Mass) Urinary output was followed hourly by means of an indwelling bladder catheter In addition most patients had a pacing catheter in the right ventricle and another catheter in the right atrium allowing measurements of central venous pressure and administration of fluids Before the institution of IABP 11 patients sustained one or several cardiac arrests requiring closed chest massage and in four of these patients resuscitation maneuvers had to be prolonged for over 1 hour In nine patients it was necessary to resort to artificial ventilation

Procedure

The counterpulsation balloon was inserted in the common femoral artery under local anesthesia and guided into the thoracic aorta under fluoroscopic control and positioned just distal to the origin of the subclavian artery The femoral artery was then sutured either directly around the catheter or through a Dacron end to side graft anastomosis [9] The balloon pump was activated with either an AVCO console or a DATASCOPE console Counterpulsation was programmed on the radial artery pressure curve so as

ptal defect was impossible owing to massive ptal necrosis and these patients died in the erating room In the other eight patients the ptal defect was corrected and all these patients covered satisfactory cardiac function Three of iese patients nevertheless died one from a current posterior septal rupture 48 hours after ie operation another from septicemia 5 weeks iter and the third from a cerebral vascular ccident during the second month following the peration The five remaining patients are long erm survivors with a follow up period ranging rom 13 to 27 months One of these patients has a minor residual left to right shunt

, Of the four patients with mitral regurgitation *lue to rupture of the* posterior papillary muscle me d ed after 36 hours from intractable ventric ilar fibrillation whereas the other three under vent prosthetic valve replacement and are living 15 to 21 months later

Influence of mortality rate Of the 24 patients in cardiogenic shock without associated mechan ical lesions 20 were treated with I A B P alone six survived more than 1 month after removal of the balloon and three are still alive after a period ranging from 13 to 31 months In the four remaining patients in whom revascularization surgery was undertaken two were still alive 15 and 18 months later The over all long term survival rate in this group of patients was 21 per cent In the group of patients in shock related to a mechanical lesion there were no survivors among the patients treated by I A B P alone even when the latter was continued for more than a week Of the 13 patients who underwent surgery 12 survived for more than 1 month and eight for more than 1 year after the operation Mean survival rate in this group was 44 per cent On the whole 13 patients out of 42 survived for more than 1 year i e 31 per cent

Complications Signs of reduced vascularization of the catheterized limb were commonly observed during the first hours of circulatory assistance However these signs regressed as the patient s circulatory status improved except in two cases in which severe and prolonged ischemia necessitated removal of the balloon The latter could not be reinserted in the contralateral limb in one patient No case of vascular insufficiency of the lower extremity was encountered after removal of the balloon Nevertheless passage of Fogarty embolectomy catheters to ensure complete patency of proximal and distal vessels was always performed following balloon removal A renal embolism was found at autopsy in one patient In another patient who died after 12 days of circulatory assist autopsy revealed aortic dissection which did not extend beyond the renal arteries During the first 48 hours the majority of patients exhibited a significant decrease in their platelet count but the latter never dropped below 100 000 per mm

Discussion

The results reported in this paper confirm the efficacy of I A B P in cardiogenic shock complicating acute myocardial infarction [1 11 6] In the absence of any associated mechanical lesion shock was reversed in 80 per cent of patients and peak improvement was generally achieved within 24 hours of initiation of I A B P This is in agreement with reports by other authors [3 3 3] In 20 per cent of patients however shock was irreversible and in these cases necropsy showed extensive infarction with diffuse coronary lesions Death appears to be inevitable in these patients whether surgery is attempted or not

In a relatively small number of cases (25 per cent) improvement was marked and stable thus allowing gradual withdrawal of balloon assist However only half of the patients survived for over 1 year Thus with I A B P alone long term survival rate remained low since it attained only 12 per cent in this series and in that of Dunkman and associates 9 per cent in the cooperative study by Scheidt and associates [1] and 10 per cent in the report by Willerson and associates [1] It is probable that myocardial lesions were less extensive in long term than in short term survivors However one short term survivor proved to have coronary lesions amenable to surgery It would thus appear preferable to perform coronary arteriography prior to removal of the balloon so as to identify patients amenable to coronary surgery

Over half the patients in this series were balloon dependent Similarly 65 per cent of the patients in the series reported by Leinbach and associates [3] could not be taken off circulatory assist This state of dependence may be due either to a combination of an infarct and ischemia partially reversible under the influence of I A B P or to extensive destruction of the myocardium Revascularization surgery can only

Table IV Summary of hemodynamic data in 18 patients with cardiogenic shock with mechanical lesions*

	HR (beats/min)	Arterial pressure (mm Hg)		PWP mm Hg		CI† L/min/M	Q/S	UO (ml/hr)
		S	M	M	V wave			
Before IABP	112	64	67	19	36	1 30	3 5	13
	12	16	12	4	5	0 30	1 2	11
During IABP (23 ± 14 hr)	100	71 (84)	68	15	28	1 90	2 8	38
	15	9 (13)	4	5	5	0 60	[illegible]	19
	< 0 001	NS NS	NS	NS	< 0 01		< 0 01	< 0 01

Q/S pulmonary systemic flow ratio (14 patients with ventricular septal defect) Other abbreviations as in Table III
†Only in the four patients with papillary muscle rupture

57 hours) The heart rate dropped from 105 ± 16 to 102 ± 15 beats per minute spontaneous systolic blood pressure rose from 83 ± 19 to 93 ± 16 mm Hg the cardiac index increased from 1 38 ± 0 39 to 2 00 ± 0 50 L/min/M and diuresis increased from 7 ± 10 to 56 ± 34 ml per hour Pulmonary artery wedge pressure fell from 22 ± 5 to 16 ± 3 mm Hg In some patients however volume replacement had to be undertaken to gain a maximal benefit from the Frank Starling mechanism

Gradual weaning was possible in six patients and the balloon was removed after 58 hours of IABP on the average However before removal of the balloon two patients underwent coronary arteriography in order to assess the possibility of subsequent myocardial revascularization (cases 4 and 8) Three of these six patients were in hospital deaths postmortem examination of one of these patients (case 10) showed that the right coronary artery was completely obstructed and that the left descending artery was stenosed over 80 per cent with a good peripheral runoff and technically possible bypass grafting

Thirteen patients remained balloon dependent Seven patients did not undergo coronarography five because of advanced age and/or evidence of extensive necrosis one patient developed acute ischemia of the catheterized limb necessitating removal of the balloon which could not be reinserted in the contralateral limb and this patient died 3 hours later the seventh patient because of recurrent shock in spite of a 12 hour circulatory assist Six patients underwent coronarography with balloon support without any incident Surgery could not be performed in two patients (cases 5 and 6) because the lesions were too extensive A coronary artery bypass graft was undertaken in four patients (cases 12 13 14 1 and in two of these an aneurysm wa ... resected Two patients died in the immedia postoperative period and two patients were lo term survivors

Group II (18 patients) After 3 to 6 hours balloon assist shock showed a tendency subside in all patients and peak improvement w achieved after a mean period of 23 ± 14 hours IABP (Table IV) The heart rate dropped fro 112 ± 12 to 100 ± 15 beats per minute Spon neous blood pressure was unchanged a pulmonary wedge pressure decreased from 19 ± 4 to 15 ± 5 mm Hg Diuresis increased f 13 ± 11 to 38 ± 19 ml per hour In the 1 patients with septal rupture (patients 1 to 14) the pulmonary/systemic flow ratio dropped from 3 5 ± 1 2 to 2 8 ± 1 7 In the four patient wi mitral regurgitation (patients 15 to 18) th cardiac index increased from 1 30 ± 0 30 to 1 90 ± 0 60 L/min/M and the pulmonary capillary V wave decreased from 36 ± 5 to 28 ± 5 mm Hg

Of the 14 patients with a septal rupture fo were not operated upon either because of age (case 10) organic renal failure (case 11) or extensive infarction of the posterior and inferior septum (cases 5 and 12) Despite maintenance of IABP for 226 ± 28 hours all these patient died In the two patients with posterior septal rupture there was massive involvement of the septum and both ventricles together with severe trivascular disease On the other hand the patient to whom surgery was refused becau e of age had a relatively limited anterior septal rupture with one vessel disease

Ten patients with a septal rupture were operated upon In two patients closure of the

previously published studies[7, 8 … 6, 17, 3] it appears that I A B P is an effective method for treating cardiogenic shock When a surgical intervention is combined with I A B P 25 to 30 per cent of the patients are potential long term survivors However the chances of survival are not the same when shock is related to extensive involvement of the myocardium and when it is due to a mechanical complication In the first eventuality myocardial lesions are irreversible in approximately 60 per cent of the cases and patients are beyond all therapeutic resources Less than half of operable patients in this category survive the operation thus leaving on the whole 20 to 25 per cent long term survivors On the other hand when shock is related to a mechanical complication surgical correction is possible in a large number of cases and the long term survival rate is close to 50 per cent

Summary

Forty two patients with cardiogenic shock (CS) secondary to myocardial infarction were treated with intra aortic balloon pumping (I A B P) In 4 patients C S was associated with ventricular septal defect (V S D) and in four with mitral regurgitation (M R) secondary to rupture of the posterior papillary muscle All patients were resistant to conventional medical therapy Shock was reversed in 20 of the 24 patients in C S without mechanical complications After 24 to 48 hours of I A B P cardiac index (C I) increased from 1 38 to 2 00 L/min/M² systolic arterial pressure (S A P) from 83 to 96 mm Hg urinary output (U O) from 10 to 56 ml per hour and pulmonary wedge pressure (P W P) decreased from 22 to 16 mm Hg Three patients treated with I A B P alone survived more than 1 year of the 13 patients who were balloon dependent four have undergone emergency surgical procedures and two were long term survivors In all patients with mechanical complications I A B P resulted in significant clinical and hemodynamic improvement P W P decreased from 19 to 15 mm Hg and U O increased from 13 to 38 ml per hour while S A P remained unchanged In patients with V S D the pulmonary/systemic flow ratio (P/S) declined from 3 5 to 2 8 in patients with M R, V" wave amplitude decreased by 8 mm. Hg Emergency surgery was performed in 10 patients with V S D and in three patients with M R and there were eight long term survivors (13 to 27 months) It is concluded that I A B P is an effective means of supporting the circulation in C.S Of the 42 patients with C S treated by combining I A B P and emergency surgery 13 (31 per cent) were long term survivors (20 ± 6 months)

REFERENCES

1 Nielsen B L and Marner I L Shock in acute myocardial infarction Acta Med Scand 175 65 1964
2 Cronin R F P Moore S and Marpole D G Shock following myocardial infarction a clinical survey of 140 cases Can Med Assoc J 93 57 1965
3 Scheidt S Ascheim R and Killip J Cardiogenic shock after acute myocardial infarction Am J Cardiol 26 6 19 0
4 Killip J and Kimball J T Treatment of myocardial infarction in a coronary care unit A two-year experience with 200 patients Am J Cardiol 20 457 19 0
5 Buckley M J Leinbach R C Kastor J A Laird J D Kantrowitz A R Madras P N Sanders C A and Austen W G Hemodynamic evaluation of intra aortic balloon pumping in man Circulation 41 (Suppl II) 130 19 0
6 Kantrowitz A Tjonneland S Freed P S Phillips S J Butner A N and Sherman J L Jr Initial clinical experience with intra aortic balloon pumping in cardiogenic shock J A M A 203 113 1968
Bergman D Goetz R H and State D Clinical experience with a new cardiac assist device J Thorac Cardiovasc Surg 62 577 1971
8 Mueller H Ayres S M Gianelli S Jr Conklin E F, Mazzara J T and Grace W J Effect of isoproterenol, L norepinephrine and intra aortic counterpulsation on hemodynamic and myocardial metabolism in shock following acute myocardial infarction Circulation 45 335 1972
9 Sanders S A Buckley M J Leinbach R C Mundth E D and Austen W G Mechanical circulatory assistance Current status and experience with combining circulatory assistance emergency coronary angiography and acute myocardial revascularisation Circulation 45 1292 1972
10 Scheidt S Wilner G and Mueller H Intra aortic balloon counterpulsation in cardiogenic shock Report of a co-operative clinical trial N Engl J Med 288 9 9 19 3
11 Willerson, J T Curry G C Watson J T Leshin S J Ecker R R Mullins C B Platt M R and Sugg W L Intra aortic balloon counterpulsation in patients with cardiogenic shock medically refractory left ventricular failure and/or recurrent ventricular tachycardia Am J Med 58 183 19 5
12 Corday E Meerbaum S and Lang T Treatment of cardiogenic shock with mechanical circulation assist Fact or fiction Am J Cardiol 30 5 5 1972
13 Leinbach R C Gold H K Dinsmore R E Mundth E D Buckley M J Austen W G and Sanders C A The role of angiography in cardiogenic shock Circulation 48 (Suppl III) 9 19 3
14 Mundth E D Buckley M J Leinbach R C De Sanctis R W Sanders C A Kantrowitz A and Austen W G Myocardial revascularization for the

be of potential benefit for patients in the former category In a few patients the extensive nature of the infarct can be easily determined from the clinical history (advanced age iterative infarcts), this was subsequently shown by the necropsy findings in five patients from this series who in the light of the data now acquired would be considered unsuitable for circulatory assist In the majority of cases, however only coronary arteriography combined with ventriculography makes it possible to identify the patients who are balloon dependent owing to persistent ischemia On the basis of the same operability criteria as those suggested by the Harvard Group eight of 13 balloon dependent patients were considered inoperable Despite maintenance of circulatory assist all these patients died and necropsy confirmed the extensive nature of the infarct (recent or long standing) destroying over 40 per cent of the ventricular myocardium These patients are beyond all therapeutic resources except perhaps for heart transplantation On the other hand revascularization was possible in 38 per cent of balloon dependent patients The proportion of operable patients was higher (58 per cent) in the series reported by Leinbach and associates[5] and this can probably be attributed to stricter patient selection criteria Revascularization of a myocardial area in which lesions are still reversible markedly improves the survival rate since 40 to 50 per cent of patients who underwent surgery were long term survivors Finally with mechanical circulatory assistance used either alone or combined with a surgical procedure 21 per cent of the patients with shock not complicated by any mechanical lesions were long term survivors These results are similar to those reported by the Boston group

I A B P induced regression of shock in all patients when this state was mainly due to a mechanical lesion This improvement results mainly from a decrease in afterload which in turn induces a reduction of the left to right shunt or of mitral regurgitation However it was not possible to achieve enough stabilization of the circulatory status of these patients to avoid the risk of early surgical intervention In view of the transient nature of the improvement surgical correction of mechanical lesions should be considered as an emergency operation In this series none of the nonoperated patients survived despite maintenance of I A B P for over 200 hours On the other hand eight of 13 patients who underwent surgery are still alive more than 1 year later

The feasibility of correction of septal ruptures depends on their location and the extent of associated lesions The five patients who underwent surgery and survived had an anterior septal rupture This result is consistent with that reported by Buckley and associates Anterior septal ruptures are secondary to obstruction of the left anterior descending artery, either alone or associated with critical stenoses of the other two major coronary arteries In the last case the survival rate may be improved by combined closure of the ventricular septal defect and coronary artery bypass On the other hand a posterior septal defect is usually subsequent to a very extensive infarct involving the entire posterior and superior part of the septum, the inferior wall of both ventricles, and often the posteromedial papillary muscle The extent of the lesion renders surgical correction an extremely difficult undertaking However successful closure of a posterior septal defect combined with prosthetic mitral valve replacement was recently reported In both anterior and posterior septal ruptures coronarography and ventriculography make it possible to determine the degree of associated lesions and the extent of irreversible myocardial damage Although emergency surgical repair of a septal rupture may be possible without the aid of circulatory assist in these cases the septal rupture was always anterior and associated with one vessel disease In cases where lesions are more extensive I A B P enables stabilization of the patient's circulatory status and provides circulatory support during angiography and the perioperative period Furthermore I A B P can theoretically preserve cerebral circulation thus avoiding central nervous system dysfunction as was the case in two out of five patients in the series reported by Killen and associates Three of the four patients with mitral regurgitation due to rupture of a posterior papillary muscle were long term survivors However in all cases the infarct was limited in size and a good surgical result might be expected Nevertheless it may be necessary to perform a coronary vein graft in addition to prosthetic valve replacement

In view of the results reported in this paper and

›ninvasive assessment of left ventricular ›nction in chronic heart disease

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›easurement of angiographic left ventricular lume and parameters derived therefrom' ring cardiac catheterization has yielded valu le insight into left ventricular function Cathe rization and angiography however continue to › associated with some risk to the patient in rms of morbidity and death Therefore they re not to be repeated multiple times in assess ent of the progression of myocardial dysfunc on

It has long been known that systolic time itervals (STI) recorded externally in man may e abnormal in the presence of heart failure he relation between such external measures and re invasively obtained index of left ventricular erformance left ventricular ejection fraction EF) has been explored with enthusiastic reports f results This study attempts to define urther the relationship between various STI and EF in a variety of types of chronic heart disease ncluding some which have been omitted from earlier studies with a particular view to the predictability of EF in an individual patient by the noninvasive approach

Patients and methods

A total of 121 patients were studied 96 by both invasive and noninvasive means and 25 by nonin vasive alone They were classified according to clinical examination as shown in Table I Decom pensation was defined clinically on the basis of evidence of congestive heart failure manifest as symptoms (N Y H A Class III or IV) cardiomeg aly and pulmonary venous hypertension (on chest x ray) Within the volume overload compensated group there were 15 patients with aortic regurgitation 17 with mitral regurgitation and three with combined aortic and mitral regur gitation two had ventricular septal defects and one an arteriovenous fistula The volume over load decompensated group consisted of nine patients with aortic and one with mitral regurgi tation The pressure overload groups were pa tients with aortic valve stenosis with the excep tion of one patient who had coarctation of the aorta and a blood pressure of 160/90 None of the patients had an aortic diastolic pressure greater than 90 mm Hg All were on medications appro priate to their condition including digitalis (in 64 patients) Patients with left bundle branch block (LBBB) were not excluded three had volume overload decompensated two had pressure over load decompensated and one had primary myocardial disease 12 patients had atrial fibrilla tion

Noninvasive measurements These were made in two phases serially on the day prior to cardiac catheterization although no specific time of day was chosen Patients were not fasting First

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treatment of cardiogenic shock complicating myocardial infarction Surgery 70 78 1971
15 Buckley M J Mundth E D Daggett W M DeSanctis R W Sanders C A and Austen W G Surgical therapy for early complications of myocardial infarction Surgery 70 814 1971
16 Dunkman W B Leinbach R C Buckley M J Mundth E D Kantrowitz A R Austen W C and Sanders C A Clinical and hemodynamic results of intra aortic balloon pumping and surgery for cardiogenic shock Circulation 46 465 1972
17 Miller M G Weintraub R M Hedley Whyte J Restall D S and Alexander M Surgery for cardiogenic shock Lancet 2 1342 1974
18 Swan H J C Forrester J S Diamond C Chatterjee J and Parmely W W Hemodynamic spectrum of myocardial infarction and cardiogenic shock A conceptual model Circulation 45 1097 1972
19 Kantrowitz A Phillip S J Butner R N Tjonneland S T and Maller J D Technique of femoral artery cannulation for phase shift balloon pumping J Thorac Cardiovasc Surg 56 219 1968
20 Leinbach R C Dinsmore R E Mundth E D Buckley M J Dunckman W B Austen W C and Sanders C A Selective coronary and left ventricular cineangiography during intra aortic balloon pumping for cardiogenic shock Circulation 45 845 1972
21 Perrault M A Sebastien I Auperin A Fr eumann B and Bouvrain Y Hematome disséquant primitif de la media de l artère coronaire Arch Mal Coeur 67 987 1974
22 Goetz R H Bregman D Esrig B and Laniado S Unidirectional intra aortic balloon pumping in cardiogenic shock and intractable left ventricular failure Am J Cardiol 29 213 1972
23 O Rourke M F Chang V I Windsor H M Shanahan M S Hickie J B Morgan J J Gunning J F Sheldon A W Hall G V Michell G Coldfarb D and Harrison D G Acute severe cardiac failure complicating myocardial infarction Experience with 100 patients referred for consideration of mechanical left ventricular assistance Br Heart J 37 169 1975
24 Selzer A Gerbode F and Kerth W J Clinical hemodynamic and surgical considerations of rupture of the ventricular septum after myocardial infar... Heart J 78 598 1969
25 Kitamura S Mendez A and Kay J M ... eptal defect following myocardial infarction J T... Cardiovasc Surg 61 186 1971
26 Buckley M J Mundth E D Da...ett W M ... H K Leinbach R C and Austen W G ... management of ventricular septal defects a... regurgitation complicatin acute myocardial infar... Ann Thorac Surg 6 598 1973
27 Graham A F Stinson E B Daly P O and H... D C Ventricular septal defects after myocardial... tion J A M A 225 708 1973
28 Daggett W M Mundth E D Gold H K Lei... R C Buckley M J and Austen W G Early re... ventricular septal defect complicatin infarct... dial infarction Circulation 49 50 (Suppl I... 1974
29 Crosby I K Craver J M Crampton R S ... J P and Wellon H A Resection of ac... ventricular aneurysm with repair of ventricular... defect after acute myocardial infarction J T... Cardiovasc Surg 70 57 19..
30 Killen D A McConnahay D R Crockett J E... W A McCallister B D and Bell H H Emer... infarctectomy and closure of ruptured interv... eptum Arch Surg 109 623 19.4
31 Negre F Chaptal I A Grolleau R Cro... Duclos D and Guitter J Fermeture d urgence... jour d une perforation septale et resection d un a... rysme antéro lateral au 10... jour de son evolut... Mal Coeur 67 1359 1974
32 Temkine J Aigueperse J Gourgon R Motte C... Bouvrain Y Reparation chirurgicale d une perfo... septale au cours d un infarctu recent (... Resultat à long terme Arch Mal Coeur 67 60...
33 Gold H K Leinbach R C Sanders C A Bu... M J Mundth E D and Austen W G I... balloon pumping for ventricular septal defect or ... regurgitation complicating acute myocardial infa... Circulation 47 1191 1973
34 Mueller H and Ayres S Invasive versus nonin... cardiac assistance in myocardial infarction shock ... (abst) Circulation 49 50 (Suppl III) 108 19.4

Table II Comparison of means for normal groups

	No	R R interval	PEP†	EMI	IMC	X + IMC	LVET
Not catheterized	25	0 823	0 093_	0 02 8	0 0365	0 0655	0.283
Catheterized	10	0 786	0 08 3	0 0_92	0 0324	0 0581	0 267
F		0 69	1 .2	0 44	1.24	2. 4	3 85

Unadjusted for R R interval
Abbreviation See text

Table III Within group means

Group	No	R R interval	PEP	EMI	IMC	X + IMC	LVET	ΔPEP‡	Log PEP/LVET	EF	EDV	EDV/m
			Noninvasive measures†							Invasive measures		
Control normal	10	0 86	0 087	0 029	0 032	0 058	0 269	−0 014	−1 13	0 62	135 0	76 0
Mitral stenosis	1	0 75	0 118	0 031	0 031	0 087	0 252	0 017	−0 6	0 54	131 0	79 0
Volume overload compensated	38	0 805	0 101	0 0_0	0 034	0 0 0	0 265	0 000	−0 9	0 59	226 0	133 0
Pressure overload compensated	10	0 843	0 084	0 034	0 024	0 051	0 302	−0 017	−1 29	0 66	137 0	78 0
Volume overload decompensated	10	0 830	0 12	0 042	0 050	0 08	0 250	0 0 7	−0 68	0 34	427 0	239 0
Pressure overload decompensated	6	0 632	0 114	0 046	0 049	0 068	0 296	0 013	−0 96	0 2	261 0	145 0
Primary myocardial disease	5	0 71	0 159	0 052	0 065	0 107	0 216	0 058	−0 29	0 18	310 0	181 0
All abnormal	86	0 94	0 110	0 035	0 037	0 0 5	0 264	0 009	–	0 52	–	–
Within group standard error	–	0 159	0 018	0 008	0 013	0 017	0 033	0 018	0 26	0 10	–	–

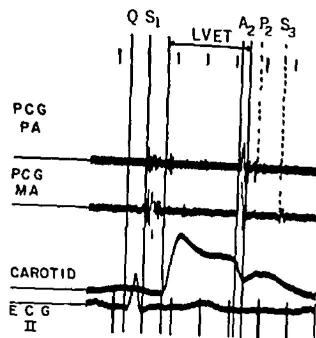
*These f es l d est m tes of missing dat obtained b w th n gro p co na e lysis f fi e pat nts Two patients in M group with EMI missing e p t t n VC group w th IMC missing one p tient in PC group w h EMI missing and on patient in PD group with IMC missing
†Adj tment f r h art rate ha been m d by o arianc n lys on th t t l sample of all p t nts so that adjusted means pert n to an av g R R interval of 0 800 in ch gr p This the a erage f th st d rd de at n f om the espect gr ups we ghted a c ding t group
‡Abbreviat o ΔPEP = observed PEP − pred cted PEP where p edicted PEP = 0 13 − (0 0 4/R R terval) Oth abbreviations See text and T bl I

the sharp upstroke of the carotid pulse wave to the dicrotic notch The Q S interval was measured from the onset of QRS to the first high frequency vibration of the first heart sound (S in Fig 1) The electromechanical interval (EMI) was measured from Q to the onset of the systolic wave of the ACG or C point (C in Fig 1) The R R interval was measured from the Q wave of the preceding complex to the Q wave initiating the systolic events being measured The duration of the QRS complex was also measured

Pre-ejection period (PEP) was calculated by subtracting LVET from Q A_2 ΔPEP was determined as the deviation of PEP from the normal as predicted by an equation modified from Weissler and associates PEP = −0 0004 (heart rate) + 0 132 To parallel the work of Garrard and associates the fraction PEP/LVET was also determined However log PEP/LVET was actually employed in analyses presented since the logarithm was found more appropriate to statistical method than the raw fraction

Isovolumic contraction time (IVC) was calculated in two ways (1) by subtraction of Q S_1 from PEP termed IMC and (2) by subtraction of EMI from PEP termed X + IMC X is therefore the interval between C and S (Fig 1)

Each recorded measurement represented the mean of five successive complexes for a patient in normal rhythm and 10 successive complexes in atrial fibrillation (with ventricular response in the range of 60 to 100 per minute) other arrhythmias were excluded Each individual measurement was made to within 5 msec by a single observer a sample series of observations was corroborated by a second observer Correction



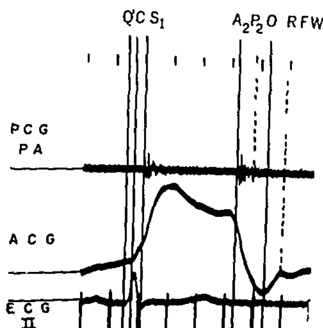


Fig 1 Noninvasive measurements Upper panel shows the carotid pulse tracing displayed together with phonocardiograms (*PCG*) in the pulmonary area (*PA*) and mitral area (*MA*) and electrocardiographic (*ECG*) Lead II Vertical lines are drawn to illustrate the onset of the cardiac cycle (*Q*) the first high frequency component of the first heart sound (*S*) the aortic component of the second heart sound (*S*) and its pulmonary component (P_2) and the third heart sound (*S*) Left ventricular ejection time (*LVET*) is denoted by vertical lines drawn at the upstroke and dicrotic notch of the carotid pulse Lower panel shows the apexcardiogram (*ACG*) displayed together with the phonocardiogram (*PCG*) from the pulmonary area (*PA*) and electrocardiographic (*ECG*) Lead II Vertical lines are drawn to illustrate the onset of the cardiac cycle (*Q*) the systolic upstroke of the *ACG* (C) and the first high frequency component of the first heart sound (*S*) the aortic and pulmonary components of the second heart sound (A_2 and P_2 respectively) the early diastolic nadir (*O*) and the rapid filling wave (*RFW*) of the ACG

Table I Patients studied

No	*Physiologic group*	*Men*	*Women*	*Mean age*	*Pr*
10	Normals with catheterization data (N)	6	4	29 9	[illegible]
25	Normals without catheterization data	10	15	22 9	[illegible]
17	Mitral stenosis (M)	3	14	38 4	[illegible]
38	Volume overload compensated (VC)	15	23	34 6	[illegible]
10	Pressure overload compensated (PC)	7	3	31 6	[illegible]
10	Volume overload decompensated (VD)	10	0	47 5	[illegible]
6	Pressure overload decompensated (PD)	5	1	54 0	[illegible]
5	Primary myocardial disease* (C)	5	0	39 0	[illegible]
121	Total	61	60	34 4	[illegible]

Decompensation was defined clinically on basis of evidence of congestive heart failure (CHF) All of the patients with primary myocardial disease showed evidence of CHF

simultaneous phonocardiogram (PCG) and electrocardiogram (ECG) with indirect carotid arterial pressure pulse were recorded in the supine 30° head up position followed by simultaneous apexcardiogram (ACG), PCG, and ECG in the [illegible] left lateral decubitus position These recordings were made on a Cambridge Instrument Company (Cambridge Mass) multichannel photographic recorder at a paper speed of 100 mm per second The PCG microphone (Cambridge Instrument Company No BM 213000 4) was placed in a position where the first heart sound (S_1) and the aortic component of the second heart sound (A_2) were clearly defined and if necessary, two microphones were used The ECG lead which showed the initial depolarization wave (Q) most clearly was monitored A Hellige transducer* with a sensitive plastic head and air filled rubber tube 4 cm long was used for both carotid pulse tracing and ACG The position of maximal apical thrust was determined by palpation prior to application of the sensing device

Total electromechanical systole QA_2 was measured from the onset of the QRS complex to the first high frequency vibration of the aortic component of the second heart sound (denoted A_2 in Fig 1) The left ventricular ejection time (LVET in Fig 1) was measured from the onset of

* Fritz Hellige and Company Freiburg West Germany This apparatus has a flat response at frequencies from 0 3 to 50 Hz and a time constant of over 3 seconds

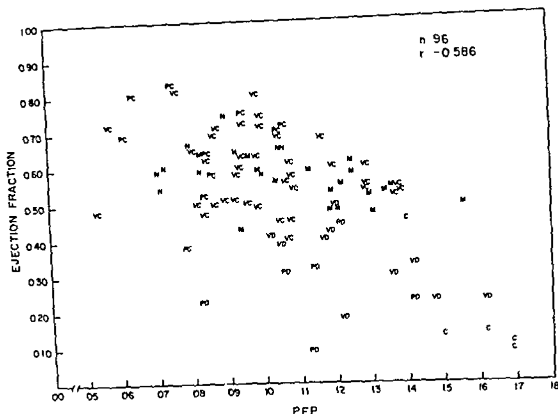


Fig. 2. The correlation between the pre-ejection period (*PEP*), unadjusted for R-R interval, and the ejection fraction. All 96 patients in whom these measurements were made are plotted using the symbols: *N* = normals; *M* = mitral stenosis; *VC* = volume overload compensated; *PC* = pressure overload compensated; *VD* = volume overload decompensated; *PD* = pressure overload decompensated; and *C* = primary myocardial disease. The correlation coefficient r = −0.586 is given at the upper right.

The sensitivity of the noninvasive parameters in discriminating abnormal from normal function within each group as compared with the sensitivity of EF was examined. Table IV shows the significance by F tests of the difference in means between normals and each abnormal group.

The ability to predict EF from the noninvasive parameters (all patients combined) was investigated by stepwise regression methods. Ejection fraction was the dependent variable, R-R interval the first independent variable, noninvasive parameter the second independent variable, and (noninvasive parameter)² the third independent variable. The best linear prediction of EF was by PEP: R = −0.586 ($\alpha > 0.01$); EF = 0.8910 + 0.0706 (R-R interval) − 3.9257 (PEP). Fig. 2 plots PEP (*unadjusted for R-R interval*) against EF in all patients, each patient is represented by a symbol for his group.

Some improvement in predicting EF from PEP was achieved by using a quadratic equation: EF = 0.3349 + 0.0454 (R-R interval) + 6.9240 (PEP) − 48.4891 (PEP)²; R = −0.630 ($\alpha < 0.01$).

It was noted that the mitral stenosis group had a longer PEP and the pressure overload compensated group a shorter PEP than expected,[7] and that the pressure decompensated group had a shorter PEP than other decompensated groups. Therefore, stepwise regression analysis for correlation of PEP with EF was repeated with these three disease groups omitted. For linear prediction: EF = 1.0582 − 0.0651 (R-R interval) − 4.4841 (PEP); R = −0.689 ($\alpha < 0.01$); and for quadratic prediction: EF = 0.2374 − 0.1226 (R-R interval) + 11.5867 (PEP) − 70.3898 (PEP)²; R = −0.774 ($\alpha < 0.01$).

If group mean values of PEP for all groups were used instead of individual patient results, then the linear prediction for EF was: EF = 0.1669 + 1.370 (R-R interval) − 5.2710 (PEP); R = 0.834. Other noninvasive parameters correlated less well with EF than did PEP.

Table IV Comparison of group means (F test)*

Groups compared	*PEP*	*FMI*	*IMC*	*\ + IMC*	*LVET*	*EF*
N vs M	18 29†	0 35	0 11	18 60†	1 5[illegible]	41[illegible]†
N vs VC	4 24‡	0 14	0 14	4 07‡	0 10	0 [illegible]1
N vs PC	0 19	1 84	2 07	0 98	4 90‡	0 69
N vs VD	23 98†	11 66†	9 26†	12 69†	1 59	41 0[illegible]
N vs PD	8 0[illegible]†	15 82†	5 77‡	1 19	2 3[illegible]	47[illegible]
N vs C	51 28†	24 70†	20 48†	27 29†	8 49†	65 00
N vs all abnormal	13 58†	3 92	1 12	8 98†	0 17	10 6[illegible]
N vs combined decompensated	39 06†	26 13†	17 24†	17 48†	1 [illegible]	79 [illegible]†

Degrees freedom for each comparison = 1 88 Group abbreviations as in Table I for other abbreviations see text
†Significant at α = 0 01 level (i e F ≥ 6 96)
‡Significant at α = 0 05 level (i e F ≥ 3 90)

Table V Within group partial correlations with ejection fraction

Group	*No*	*FMI*	*\ + IMC*	*IMC*	*PEP*	*ΔPEP*	*Log (PEP LVET*
Normal	10	−0 431	0 621	0 3[illegible]3	0 440	0 436	0 3[illegible]
Combined decompensated groups	21	−0 307	−0 516†	−0 624‡	−0 5[illegible]9‡	−0 5[illegible]1‡	−0 [illegible]
All abnormals	86	−0 512‡	−0 420‡	−0 [illegible]82‡	−0 [illegible]84‡	−0 590‡	−0 46[illegible]‡
All abnormals except M PC PD	53	−0 5[illegible]5‡	−0 566‡	−0 638‡	−0 697‡	−0 704‡	−0 [illegible]‡

Adjusted to R R interval = 0 8 Abbreviations as in text and Table I
†Significant at α = 0 05 level
‡Significant at α = 0 01 level

was made for deviations of paper speed from 100 mm per second but these were never more than 4 mm per second

Invasive measurements Left ventricular angiocardiography was performed at the time of full cardiac catheterization with biplane roll films at six per second for 5 seconds Routine cardiac medications were not discontinued for these measurements Ventricular volume was determined by the area length method of Dodge and associates [12] The opacified left ventricular cavity was outlined on each film Chamber areas were planimetered electronically and the longest chamber lengths hand measured The data were handled by computer methods described by Rackley and associates [13] incorporating appropriate x ray magnification and statistical corrections, and yielding a composite plot of left ventricular volume timed with respect to the onset of the preceding QRS Mean values for end diastolic volume (EDV) and end systolic volume (ESV) were obtained from three to six cardiac cycles Ejection fraction was calculated as (EDV ESV)/EDV Both the noninvasive and invasive data were analyzed by multiple regression methods[14, 15] outlined in more detail in the Results section

Results

Since the available number of normal subjects with catheterization data was small it was considered necessary to verify the normality of STI in this group by comparison with a larger number of normal subjects with only noninvasive data Results of the comparison, made by a simple one way analysis of variance are shown in Table II There was no significant difference between the two normal groups for any measured parameter (α > 0 10)

Systolic time intervals and EF in the catheterized normals and various abnormal groups are tabulated in Table III For this purpose the mean value of each noninvasive parameter was adjusted to an R R interval of 0 8 with a simple analysis of covariance model with R R' interval as covariable STI in patients with LBBB were not found to be longer than in patients with normal QRS duration within the same disease group LBBB occurred only in patients in the decompensated groups

l seem inappropriate to omit patients with 3 on the basis of the above findings and on practical basis of a need to assess such nts and compare them to others

e ability of the noninvasive parameters to minate abnormal from normal function as pared with EF varied with each noninvasive meter and with each disease group (Table On a group basis the discriminatory ability EP was better than that of other noninvasive meters studied but the sensitivity of PEP did always parallel that of EF

EP also tended to correlate better with EF did its subcomponents Nevertheless the tionship between PEP and EF although ificant statistically was not always close n individual patients were considered (Fig 2) is the predictability of ejection fraction from I is limited and therefore clinical usage is essarily restricted Various approaches were d to try to improve the value of STI in dicting ejection fraction By using the adratic function of PEP rather than the linear the correlation was improved slightly This provement however was judged not to be lpful in the clinical situation Following the ggestion of Garrard and associates[9] ΔPEP was aluated but this parameter correlated with EF better than raw PEP The compensated pressure overload decompensated pressure overload d mitral stenosis groups presented pre ejection riods that correlated poorly with EF When ese three group were omitted from analysis rrelation was improved only to R = −0 689

Weissler and associates showed that in heart ilure prolongation of PEP was paralleled by hortening of LVET and later Weissler and co orkers[7] suggested on this basis that the fraction PEP/LVET is a sensitive reflection of clinical eart failure Our results using the logarithm of his fraction which was more appropriate to our tatistical methods showed less good correlation with EF than raw PEP although the level of significance was the same Finally when group means instead of individual patient results were used PEP did correlate well with EF but such predictability is not useful for individual patients McConahay and associates also showed poor predictability of EF from STI including PEP and PEP/LVET in a series of normal persons and patients with coronary artery disease

These results differ from those of Garrard and associates[9] Kroetz and co workers[8] and Aronow and associates[10] who studied a variety of chronic cardiac diseases and obtained excellent correlations between noninvasive measures and ejection fraction The disease groups examined however, also differed Aronow and associates' investigated only patients with ischemic heart disease None of these studies included patients with aortic valve stenosis Weissler and associates suggested that changes in STI induced by heart failure may be masked in aortic valve disease In our study PEP was shorter in the pressure overload groups both compensated and decompensated than in corresponding volume overload groups whereas EMI did not differ significantly between these two compensated groups or between these two decompensated groups The diastolic blood pressure an important factor in afterload with respect to PEP[9] was lower in the volume overload groups (results not presented) this would favor a shorter PEP in those groups as reported by Parisi and associates[31] or the opposite of what we found But we also observed that PEP was significantly related to ventricular volume The fact that EDV was smaller with pressure overload than volume overload even when decompensation was present (Table III) may have accounted for the lesser degree of PEP prolongation in the former groups Patients with pressure overload (aortic stenosis) are well known to have prolonged LVET[32] The present study demonstrated that with decompensation in pressure overload LVET shortens less and PEP lengthens less than in other decompensated states (Table III) Thus the quotient of PEP/LVET was not a sensitive indicator of decompensation in aortic stenosis in this study

We studied 17 patients with severe mitral stenosis (mean valve area 0 98 cm) Pre ejection period was longer than expected in these patients and appeared to overestimate decreases in ejection fraction (Table IV) The PEP prolongation was seen to be due to a long C S_1 time (X) which is typical of severe mitral stenosis[26] and as expected the most severely affected patients had the longest PEP and the longest X + IMC Our results support those of Aronow and associates[33] who used IMC (called EICT in their paper) to relate to left ventricular function qualitatively instead of PEP because of the latter s excessive prolongation These findings emphasize the value of analyzing the subcomponents of PEP in some

Also, within each group of patients and within combined abnormals and combined decompensated groups, partial correlation coefficients of ejection fraction with each of the noninvasive measures were determined with the stepwise regression model previously employed None of the correlations reached statistical significance and therefore results are not stated with the exception that in the decompensated volume overload group for PEP versus EF $R = -0.665$ ($\alpha < 0.05$), and for log PEP/LVET versus EF $R = -0.684$ ($\alpha < 0.05$) Table V shows the partial correlations within the combined abnormals and combined decompensated groups

To examine the influence of ventricular volume stepwise regression methods were again employed to compute within group partial correlations for PEP with EDV and PEP with EDV/m These did not reach statistical significance in separate disease groups but did so where all abnormals were considered together for PEP with EDV $R = 0.348$ ($\alpha < 0.01$) and for PEP with EDV/m $R = 0.368$ ($\alpha < 0.01$) Table III shows the within group mean values of EDV and EDV/m

Discussion

It has been suggested that STI are useful indicators of ventricular function [11] It is well known however that there are many determinants of STI These have been demonstrated experimentally by Wallace and associates [16] Harley and co workers [1] and Talley and associates[17] and have been reviewed in detail by Aronow and associates [10] To investigate their clinical usefulness in the present study STI have been correlated with ejection fraction which although not an absolute index of contractility has been widely accepted as a parameter of left ventricular function [1,3]

The usefulness of STI is dependent on various technical and practical considerations Measurement accuracy has been found to be within 5 msec [9] In the present study within patient variability was noted to be sufficiently small to require measurement of no more than five complexes except in atrial fibrillation where measurement of 10 was necessary Respiratory variation did not seem to be important Leighton and associates[19] also observed no influence of respiration on left heart STI When LVET is measured it is necessary to use an apparatus for graphic recording of the carotid pulse with a l[...] time constant so that the duration of deflectı[...] faithfully maintained and the ejection time ıs [...] underestimated The Hellige apparatus used [...] this study has a time constant of over 3 seco[...] and hence met these criteria Use has been m[...] of the apexcardiogram in this study to de[...] subcomponents of PEP further The s[...] upstroke of the ACG, C point has been shown [...] coincide with left ventricular pressure upstroke [...] Thus the EMI and preisovolumic contrac[...] period X can be clearly defined as well as [...] carotid upstroke corrected for delay (IMC [...] Kumar and Spodick suggested that IVC [...] measured most accurately externally [...] PEP – EMI The groups of Metzger and as[so]ciates [3] and Martin and associates [4] both us[ed] external IMC for IVC and found less good cor[re]lation between external IMC and internal I[...] than between external and internal PEP B[...] pointed to the omission of the preisovolum[ic] interval X from external IMC and used this [...] explain the less satisfactory correlation Th[...] interval X is normally short but it may becom[e] prolonged in mirtal valve disease [6]

The influence of the preceding R R inter[val] although small on PEP and its subcompone[nts] was incorporated into all analyses

The patients were studied while still on appr[o]priate medications Digitalis has been shown [...] Weissler and associates [7,8] to shorten STI espe[...]cially PEP both in heart failure and in norm[al] subjects It is impractical however to disco[n]tinue such medications for up to 1 month prior to noninvasive assessment In both normal subject[s] and patients we did not employ the fasting state nor were the noninvasive studies carried out at a fixed time of day Patients with LBBB and atrial fibrillation were included Thus the rigid criteria for study used by Weissler and associate [...] were abandoned in favor of practical considerations in the hope that the method might be widely applied in the assessment of outpatients on a serial study basis as well as immediately prior to cardiac catheterization These criteria were not applied vigorously in the studies of Garrard and associates[9] and Aronow and co workers [10] but patient[s] with LBBB were excluded When LBBB exi[s]te[d] in the present study as it did only in the decom[...]pensated groups no difference was noted in ST[I] between patients with and without bundl[e] branch block within each disease group Thu[s] [...]

seem inappropriate to omit patients with on the basis of the above findings and on actical basis of a need to assess such s and compare them to others

ability of the noninvasive parameters to inate abnormal from normal function as red with EF varied with each noninvasive eter and with each disease group (Table n a group basis the discriminatory ability ? was better than that of other noninvasive eters studied but the sensitivity of PEP did ways parallel that of EF

? also tended to correlate better with EF did its subcomponents Nevertheless the onship between PEP and EF although cant statistically was not always close individual patients were considered (Fig 2) the predictability of ejection fraction from is limited and therefore clinical usage is sarily restricted Various approaches were to try to improve the value of STI in cting ejection fraction By using the ratic function of PEP rather than the linear the correlation was improved slightly This ovement however was judged not to be ful in the clinical situation Following the estion of Garrard and associates [9] ΔPEP was uated but this parameter correlated with EF etter than raw PEP The compensated pres overload decompensated pressure overload mitral stenosis groups presented pre ejection ods that correlated poorly with EF When e three groups were omitted from analysis elation was improved only to $R = -0.689$

eissler and associates showed that in heart ure prolongation of PEP was paralleled by rtening of LVET and later Weissler and co kers suggested on this basis that the fraction P/LVET is a sensitive reflection of clinical rt failure Our results using the logarithm of s fraction which was more appropriate to our tistical methods showed less good correlation h EF than raw PEP although the level of nificance was the same Finally when group ans instead of individual patient results were d PEP did correlate well with EF but such edictability is not useful for individual patients cConahay and associates also showed poor edictability of EF from STI including PEP and EP/LVET in a series of normal persons and tients with coronary artery disease

These results differ from those of Garrard and associates Kroetz and co workers [8] and Aronow and associates [10] who studied a variety of chronic cardiac diseases and obtained excellent correlations between noninvasive measures and ejection fraction The disease groups examined however also differed Aronow and associates[1] investigated only patients with ischemic heart disease None of these studies included patients with aortic valve stenosis Weissler and associates suggested that changes in STI induced by heart failure may be masked in aortic valve disease In our study PEP was shorter in the pressure over load groups both compensated and decompensated than in corresponding volume overload groups whereas EMI did not differ significantly between these two compensated groups or between these two decompensated groups The diastolic blood pressure an important factor in afterload with respect to PEP was lower in the volume overload groups (results not presented) this would favor a shorter PEP in those groups as reported by Parisi and associates [3] or the opposite of what we found But we also observed that PEP was significantly related to ventricular volume The fact that EDV was smaller with pressure overload than volume overload even when decompensation was present (Table III) may have accounted for the lesser degree of PEP prolongation in the former groups Patients with pressure overload (aortic stenosis) are well known to have prolonged LVET The present study demonstrated that with decompensation in pressure overload LVET shortens less and PEP lengthens less than in other decompensated states (Table III) Thus the quotient of PEP/LVET was not a sensitive indicator of decompensation in aortic stenosis in this study

We studied 17 patients with severe mitral stenosis (mean valve area 0 98 cm) Pre ejection period was longer than expected in these patients and appeared to overestimate decreases in ejection fraction (Table IV) The PEP prolongation was seen to be due to a long C S time (X) which is typical of severe mitral stenosis and as expected the most severely affected patients had the longest PEP and the longest X + IMC Our results support those of Aronow and associates who used IMC (called EICT in their paper) to relate to left ventricular function qualitatively instead of PEP because of the latter s excessive prolongation These findings emphasize the value of analyzing the subcomponents of PEP in some

disease states In our patients with mitral stenosis since LVET shortened whereas PEP lengthened (Table III), it is not surprising that we found poor correlation between PEP/LVET and EF Garrard and associates and Kroetz and associates [8] on the other hand found close correlation for PEP/LVET and PEP, respectively with EF but neither group stated the severity of the mitral stenosis studied

Considering our patients with compensated volume overload as a group PEP and X + IMC overestimated the reduction in EF (Table IV) These results were influenced by the large number (17) with pure mitral regurgitation in whom PEP and X + IMC were longer and LVET shorter, than in the 15 with pure aortic regurgitation In this respect Garrard and associates[7] found a poor correlation of PEP/LVET with EF in mitral regurgitation The large proportion of mitrals also contributes to the difference between our results for the entire volume overload compensated group and those published by Parisi and associates[11] for aortic regurgitation alone where PEP was shorter than normal and LVET prolonged A comparison between aortic and mitral regurgitation was not meaningful in our volume overload decompensated group as only one patient had mitral regurgitation the remainder all had aortic regurgitation

We did not study patients with severe nonrheumatic mitral regurgitation Sutton and associates[11] have shown that LVET is always short in this condition even in the presence of a normal ejection fraction and correlation between PEP/LVET and EF is poor

In conclusion our data show that in some disease states STI are able to discriminate abnormal from normal function However even on a group basis the discriminatory ability does not always parallel that of ejection fraction Furthermore on an individual basis and with less strict but more widely applicable conditions for the recording of STI the ability of STI to predict EF in chronic heart disease has been demonstrated to be poor Weissler[15] has argued recently that attempts at such predictions are unjustified in that STI ' provide measures of cardiac performance which are not the same as other hemodynamic variables but which deviate from normal at the same time and in parallel with other hemodynamic measures ' This study fails to support this view and suggests that caution should be applied in evaluating ventric performance by STI in an individual patient

Summary

Externally recorded STI were compared w invasively determined EF in 10 normal sub and 86 patients with various forms of chr heart disease From phono apex and electr diograms and carotid pulse tracings recor without rigidly controlled conditions (po sorptive state fixed time of day exclu atrial fibrillation and discontinuation of car drugs) PEP, electromechanical interval iso lumic contraction period and LVET w measured and ΔPEP (deviation from predict normal) and PEP/LVET were derived EF w determined with biplane angiocardiograp methods Patients were divided into groups b on pathophysiology and state of clinical com pensation

The ability of STI to discriminate abnorm from normal function as compared with EF varied with each noninvasive parameter and w each physiologic group On a group basis, th discriminatory ability of PEP was better th that of other noninvasive parameters studied b did not always parallel that of EF PEP al tended to correlate better with EF than the oth noninvasive measurements On an individu patient basis however the ability of even PEP predict EF was poor It is concluded th t the usefulness of assessing left ventricular function in chronic heart disease by STI is limited

REFERENCES

1 Dodge H T Sandler H Baxley W A and Hawle R R Usefulness and limitations of radiograph methods for determining left ventricular volume Am J Cardiol 18 10 1966
2 Miller G A H Kirklin J W and Swan H J C Myocardial function and left ventricular volumes in acquired valvular insufficiency Circulation 31 3 1965
3 Bunnell I L Grant C and Greene D G Left ventricular function derived from the pressure volum diagram Am J Med 39 881 1965
4 Beckmann C H and Dooley B Complications of left heart angiography A study of 1 000 consecutive cases Circulation 41 825 1970
5 Participating Laboratory Directors Swan H J C and Braunwald E editors Cooperative study of cardiac catheterization Circulation 37(Suppl III) 1968
6 Blumberger K Die Untersuchung der Dynamik de Herzen beim Menschen Ergebn Med Kinderheilk 62 424 1942
7 Weissler A M Harris W S and Schoenfeld C D Systolic time intervals in heart failure in man Circulation 37 149 1968

roetz F W Kioschos M Mozena D and Shierholz Correlation of left ventricular pre-ejection period with eft ventricular ejection fraction in patients with heart lisease (abst) J Lab Clin Med 74 971 1969

arrard C L Weissler A M and Dodge H T The elationship of alterations in systolic time intervals to jection fraction in patients with cardiac disease Circu ation 42 455 19 0

Aronow W S Bowyer A F and Kaplan M A External isovolumic contraction times and left ventric ular ejection time/external isovolumic contraction time ratios at rest and after exercise in coronary heart disease Circulation 43 59 1971

Ahmed S S Levinson G E Schwartz C J and Ettinger P O Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man Circulation 46 559 1972

Dodge H T Sandler H Ballew D H and Lord J D Use of biplane angiocardiography for the measurement of left ventricular volume in man Am Heart J 60 76? 1960

Ra klev C E Hood W P Jr Cleveland L and Stacy R W Derivation of cardiac mechanical parameters from serial biplane angiocardiograms J Appl Physiol. 24 259 1968

Draper N R and Smith H Applied Regression Anal ysis, New York, 1966 John Wiley & Sons

Graybill F A An Introduction to Linear Statistical Models, New York 1961 McGraw Hill Book Company Inc

Wallace A G Mitchell J H Skinner N S and Sarn ? S J Duration of phases of left ventricular systole Circ Res 12 611 1963

Harey A Starmer C E and Greenfield J C Jr Pressure flow studies in man An evalua ion of the duration of the phases of systole J Clin Invest 48 895 1969

Tal ey R C Meyer J E and McNay J L Evaluation of the pre-ejection period as an estimate of myocardial contra tility in dogs Am J Cardiol 27 384 1971

Leighton R F Weissler A M Weinstein P B and Wooley C F Right and left ventricular systolic time intervals Effects of heart rate respiration and atrial pacing Am J Cardiol 27 66 1971

Craige E Clinical value of apex cardiography Am J Cardiol 28 118 19 1

Willems J L DeGeest H and Kesteloot H On the value of apex cardiography for timing intracardiac events Am J Cardiol 28 59 19 1

Kumar S and Spodick D H Study of the mechanical events of the left ventricle by atraumatic techniques Comparison of methods of measurement and their signif icance Am Heart J 80 401 1970

23 Metzger C C Chough C B Kroetz F W, and Leonard J J True isovolumic contraction time Its correlation with two external indices of ventricular performance Am J Cardiol 25 434 1970

24 Martin C E Shaver J A Thompson M E Roddy P S and Leonard J J Direct correlation of external systolic time intervals with internal indices of left ventricular function in man Circulation 44 419 1971

25 Coghlan C, Prieto G and Harrison T R Movements of the heart during the period between the onset of ventricular excitation and the start of left ventricular ejection Am Heart J 62 65 1961

26 Oreshkov V I Isovolumic contraction time and isovo lumic contraction time index in mitral stenosis Study on basis of polygraphic tracing (apexcardiogram phonocar diogram and carotid tracing) Br Heart J 34 533 1972

27 Weissler A M, and Schoenfeld C D Effect of digitalis on systolic time intervals in heart failure Am J Med Sci 259 4 1970

28 Weissler A M Kamen A R Bornstein R S Schoen feld C D and Cohen S The effect of deslanoside on the duration of the phases of ventricular systole in man Am J Cardiol 15 153 1965

29 Weissler A M Harris W S and Schoenfeld C D Bedside technics for the evaluation of ventricular func tion in man Am J Cardiol 23 577 1969

30 McConahay D R Martin C M and Cheitlin M D Resting and exercise systolic time intervals Correlations with ventricular performance in patients with coronary artery disease Circulation 45 592 1972

31 Parisi, A F Salzman S H, and Schechter E Systolic time intervals in severe aortic valve disease Changes with surgery and hemodynamic correlations Circulation 44 539 1971

32 Weissler A M Peeler R G, and Roehll W H Relationships between left ventricular ejection time stroke volume and heart rate in normal individuals and patients with cardiovascular disease Am Heart J 62 3? 1 ?

33 Aronow W S Kaplan M A and Ellerlad M H LVET/EICT ind x in mitral valve disease Acta Cardiol 26 1 19 1

34 Sutton G C, Chatterjee K and Caves P K Diagnosis of severe mitral regurgitation due to non rheumatic chordal abnormalities Br Heart J 35 877 1973

35 Weissler A M Resting and exercise systolic intervals (letter) Circulation 46 633 1972

The fourth heart sound in patients without demonstrable heart disease

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In 1971, two published abstracts[1] suggested the common occurrence of audible and phonocardiographically recordable fourth heart sounds in subjects without evidence of cardiovascular disease Since that time various papers editorials and letters have appeared[1 11] supporting or refuting the original observations One of the abstracts[1] has been cited frequently[1 *] during the course of this controversy because it supplied data from patients subjected to cardiac catheterization The manuscript which provided information for the abstract had been submitted for publication on a date which anteceded appearance of the above mentioned references As anticipated, the paper created editorial shock waves and was rejected It is apparent that other investigators[4 5 9] have been impressed with the presence of low frequency presystolic sounds heard in otherwise healthy subjects judged to be normal on the basis of history physical examination and noninvasive data We report here our observations on the prevalence of audible and phonocardiographically demonstrable fourth heart sounds in a group of patients with normal hearts diagnosed by right and left heart catheterization and selective coronary cineangiography

Material and methods

One hundred consecutive patients comprised the study group There were 55 men and 45 women whose ages ranged from 17 to 67 with a mean of 43 years All patients were subjected to cardiac catheterization because of atypical che pain systolic heart murmurs, or non pecifi ele trocardiographic changes originally thought b their referring physicians to possibly repre heart disease Patients with electrocardiograph evidence of ventricular pre excitation syndrom idiopathic bundle branch block, or first-degre atrioventricular block were not included Also excluded were patients with significant extraca diac abnormalities such as anemia and thyr toxicosis

All patients were evaluated with a complete history physical examination, posterior anter and lateral chest roentgenograms 12 lead scalar electrocardiogram, Frank vectorcardiogram sero logic test for syphilis complete blood count and urinalysis The group consisted of all adu subjects diagnosed as normal on the basis of complete right and left heart catheterization performed in this laboratory during the period 1968 to 1971

Cardiac catheterization All subjects were studied in the postabsorptive nonsedated state in the supine position With the use of local anes thesia with 1 per cent lidocaine, the brachial artery and an antecubital vein were isolated No 7 or 8 catheters connected to two P23Db Statham strain gage transducers were advanced from the artery and vein to the left and right heart respectively where pressure measurements were obtained from the superior vena cava righ atrium right ventricle main pulmonary artery pulmonary arterial wedge position aorta and left ventricle Selective right and left coronar arteriograms were performed with 75 per cen Hypaque according to the Sones technique In addition to 48 frames per second cineangiographi evaluation rapid sequence 14 by 14" roentgeno grams of each coronary artery were obtained at a

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of six exposures per second during coronary on Both coronary arteries were opacified right anterior and left anterior oblique tions, and an average of 12 coronary injec were performed in each patient Right heart ntricular and aortic angiograms were also ed with 75 per cent Hypaque as a contrast um Cardiac output was determined by the t Hamilton method with the use of indocy green (Cardiogreen) central injection and ling sites Selective dye dilution curves and d selective hemoglobin oxygen saturation were obtained from any patient thought to a murmur possibly indicative of a left to shunt at the great vessel atrial or ventric level All patients with the differential diag s of hypertrophic subaortic stenosis were her evaluated with isoproterenol infusion and iced ventricular premature contractions dur simultaneous and continuous monitoring of ventricular and descending aortic or femoral rial pressures All data were recorded in a 12 Electronics for Medicine light beam oscil opic photographic recorder at various paper eds The following hemodynamic calculations e computed Cardiac index (L /min /M²) oke volume (ml /beat) stroke index (ml /beat/ ²) peripheral arterial pulmonary arterial and lmonary arteriolar resistance (dyne sec /) corrected ejection time (msec) tension ne index (mm Hg sec /min) ventricular power g M /min /M²) stroke power (Gm M /sec / ²) and in most cases first derivative of left ntricular pressure (mm Hg/sec)

Phonocardiography Phonocardiograms were tained from all patients in a sound proof vibra ion free room especially designed for this urpose In most cases the tracings were taken he day prior to cardiac catheterization studies he patients were studied in a supine position our bell type Leatham microphones (Cambridge o) were affixed to the anterior chest at the mitral, tricuspid pulmonic and aortic areas utilizing rubber bulb-aspirated suction Simulta neous recordings of all these four areas were made during end-expiration at a frequency range of 50 to 500 cycles per second and with settings at 6 12 and 18 decibels per octave An average of 17 phonocardiographic recordings and at times various pulse tracings were obtained from each patient in a DR-8 Electronics for Medicine light beam oscilloscopic photographic apparatus using four phonocardiographic channels with a simultaneously recorded electrocardiographic lead

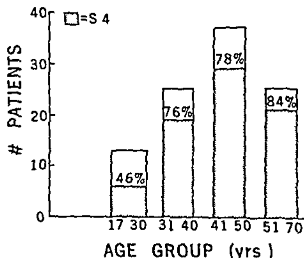


Fig 1 Number of patients studied within each age group and percentage of patients in each group with recordable fourth heart sounds (*S-4* = fourth sound)

A fourth heart sound was defined as any appreciable and discrete vibration occurring after the P wave but beginning before the QRS of an electrocardiogram

Auscultation Cardiac auscultation was performed at the bedside during the course of admission physical examination prior to cardiac catheterization and following the procedure Fourth heart sounds were recognized as low pitched vibrations distinct from and preceding high frequency sounds which included the first heart sound or any successive audible systolic components Other qualities of the fourth heart sounds so heard were (1) maximum audibility with light application of the stethoscope bell and (2) diminution of fourth heart sound intensity with the patient in an upright position In order to further evaluate the bedside findings patients were also examined in the recording room High gain oscilloscopic displays of the recorded sounds and a simultaneous Lead II of the electrocardiogram were noted Direct observation of these vibrations during concurrent auscultation enabled confirmation of the presystolic character and timing of the lower frequency fourth heart sound

Results

Seventy five of these 100 subjects without evidence of heart disease had a recordable fourth heart sound There were 42 men and 33 women

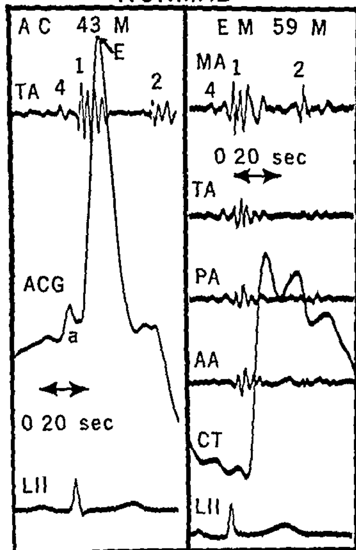


Fig 2 Examples of phonocardiograms recorded Note the discrete fourth heart sounds recorded prior to the onset of the QRS (*LII* = Lead II *MA* = mitral area *TA* = tricuspid area *PA* = pulmonic area *AA* = aortic area *CT* = carotid pulse tracing *ACG* = apexcardiogram)

whose ages ranged from 17 to 67 with a mean of 44 years The prevalence of recordable fourth heart sounds was highest in the 50 to 70 year old age group and lowest in those whose age was between 17 and 30 (Fig 1) Typical examples of recordings obtained are shown in Fig 2

A fourth heart sound was audible at the mitral and/or tricuspid areas in 80 per cent (60/75) of patients with this sound on the phonocardiogram

Discussion

The data set forth in this study indicate that a phonocardiographically recordable fourth heart sound is found in 75 per cent of patients without catheterization evidence of heart disease Since all subjects had either atypical chest systolic murmurs or nonspecific electrocardiographic changes, it can be argued that they were in fact 'abnormal and had some forms of heart disease which might not be identified by the techniques employed in this study S Quarry[5] found a remarkably similar prevalence (73 1 per cent) of recordable fourth heart sounds in ambulatory subjects without signs or symptoms of heart disease It is possible that some of these latter patients had undetected heart disease which might have been discovered by invasive study Given these limitations it is probable that both groups can be considered to be free of definable cardiac disease Tavel has likewise recorded a fourth heart sound in 75 per cent of normal subjects

The issue of fourth heart sound audibility in normal subjects is unsettled and undergoing vigorous debate Our original manuscript evoked the following editorial response The list of clinicians who state that they rarely hear atrial sounds in normal subjects is most impressive These people have listened to thousands of hearts it is inconceivable that they miss 60 atrial sounds for every 100 patients they examine S seeming blundering on the part of these clinicians requires some reasonable explanation Fou and Adolph[4] suggested that audible splitting of the first heart sound found in 83 per cent of normal adults might account for the false impression of a fourth heart sound-first heart sound sequence Other combinations such as first heart sound-ejection click might similarly mimic a fourth sound followed by a first sound on auscultation Despite such possibilities recently published data indicate that the ear not uncommonly perceives what probably is a fourth heart sound in patients without heart disease Currently there is no technique which graphically displays presystolic sounds that can unequivocally be considered to cross the threshold of audibility A prospective blind polygraphic investigation by Rectra and associates suggested that the relative amplitude and frequency of the fourth heart sound were not significantly related to its detection on auscultation

It is our impression that patients with demonstrable cardiac disease have louder fourth heart sounds than those heard in otherwise normal subjects We have not performed a blind controlled study in order to ascertain whether or

nowledge of ancillary clinical or hemo
ic features in such cases creates bias in
tation and such investigation is being
aken In order to evaluate the significance
urth heart sound in an individual patient
bedside diagnostic procedures might be
yed A prominent presystolic impulse
ble at the cardiac apex and confirmed by a
a wave on an apexcardiogram is in most
indicative of heart disease [3] These tech
s, however must be periodically re evalu
and their diagnostic sensitivity or accuracy
mined by comparison with results secured
normal subjects To our knowledge no
olled prospective investigation has been
rmed in order to determine (1) the accuracy
ical palpation when auscultation and/or
y are not known or (2) the sensitivity and
ficity of combined palpation and ausculta
by master clinicians in a similar setting when
ed accurate hemodynamic and angiographic
are available but unknown to the examiner
l such study has been accomplished the
cal significance assigned to the fourth heart
d will remain unclear

mary

ne hundred patients 17 to 67 years of age had
mal hearts diagnosed on the basis of complete
it and left heart catheterization and coronary
angiography Phonocardiograms were ob
ed from each patient providing an average of
recordings per subject for analysis 75/100 (75
cent) subjects had a recordable fourth sound
75 (80 per cent) of the latter group had an
ible fourth heart sound

It is concluded that recordable and audible fourth heart sounds are common findings in subjects without catheterization evidence of cardiovascular disease

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REFERENCES

1 Benchimol A and Desser K B The fourth heart sound in patients with proven normal hearts Circulation 43 (Suppl II) 140 1971
2 Spodick D H Rectra E Kahn A et al Audibility of the fourth heart sound A prospective blinded investigation Circulation 43 (Suppl II) 33 1971
3 Spodick D H and Quarry Pigott V M Fourth heart sound as a normal finding in older persons N Engl J Med 288 140 1973
4 Fowler N O, and Adolph R J Fourth sound gallop or split first sound (Letter) Am J Cardiol 31 531 1973
5 Spodick D H and Quarry V M Prevalence of the fourth heart sound by phonocardiography in the absence of cardiac disease Am Heart J 87 11 1974
6 Spodick, D H The fourth heart sound (Letter) Tavel, M (Response) Circulation 49 1263 1974
7 Prakash R Aytan N Dhingra R et al Variability in the detection of a fourth heart sound—its clinical significance in elderly subjects Cardiology 59 49 1974
8 Ferrero C Scherrer J R and Vaudaux B P Un critère d auscultation typique du galop presystolique Schweiz Med Wochenschr 104 1558 1974
9 Rectra E H Kahn A H Pigott V M et al Audibility of the fourth heart sound A prospective blind auscultatory and polygraphic investigation J A M A 221 36 1972
10 Fowler N O and Adolph R J Fourth sound gallop or split first sound? Am J Cardiol 30 441 1972
11 Tavel, M E The fourth heart sound—a premature requiem? (Editorial) Circulation 49 4 1974
12 Benchimol A and Dimond E G The apex cardiogram in normal older subjects and in patients with arteriosclerotic heart disease Effect of exercise on the "a wave Am Heart J 65 789 1963
13 Benchimol, A and Dimond E G The apex cardiogram in ischemic heart disease Br Heart J 24 581 1962

Myocardial infarction and rupture of the heart
A macroscopic pathologic study

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The early descriptions by Harvey[1] and Morgagni of cardiac ruptures in the acute stage of myocardial infarctions have been followed by intensive research though purely anatomical studies have been relatively limited in number[3,5] Contemporary developments in the field of cardiac reanimation and emergency surgery in cases of myocardial infarction can be shown to be relatively efficient against this dreadful complication the cause today of the death of many patients in the acute phase of myocardial necrosis

Material and methods

The 68 cases of rupture of the heart following infarction—all of them transmural (Group I)—were compared to an equal number of transmural myocardial necrosis without cardiac rupture (Group II) (The selection of patients for Group II was made absolutely at random from the 1 131 necropsies of patients who died from heart disease performed from 1965 to 1974 inclusive)

The macroscopic pathological studies were carried out according to the following procedure (1) examination of the pericardial sac aspect and weight of a possible hemopericardium weight of the heart (in grams) extent of left ventricular hypertrophy (the thickness of the left ventricle in millimeters) was measured at the top left rim of the heart columnae trabeculae cordis excluded less than 13 mm no left ventricular hypertrophy (LVH) from 13 to 17 mm moderate LVH (+) from 18 to 22 mm severe LVH (++) more than 22 mm considerable LVH (+++) (2) examination of the various valvular systems (3) search for a possible heart rupture and analysis of elements (location course dimensions) (4) serials of the myocardium (thickness approximately 2 mm) (5) location size depth limits of the myocardial necrosis and age of myocardial infarct

The same method was used to describe old infarcts if any or elements of older fibrosis The coronary arteries were first examined through cross sections made with the lancet every 2 mm or so then opened longitudinally with scissors The location importance and length of the coronary stenosis were recorded and quantified for only those occlusions equal or greater than 50 percent of the arterial lumen were retained as significant The results were then transferred to tables The location length number and age of all possible coronary thromboses were also recorded The criteria described in a previous paper were retained to appreciate the *strictly anatomical possibilities* of performing a direct myocardial revascularization In view of their insufficient number (29 out of the 136 necropsies), the coronary angiographic postmortem results were not used

All measurable data were submitted to statistical analysis (chi square test—corrected)

Results

Ruptures of the heart may be a precocious accident (a third of the cases before the twenty fourth hour) but semi late or late rupture are

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Time distribution of rupture through the walls			
Day	No	Per cent	
1	18	34	43
2	5	9	
3	4	8	
4 to 7	16	30	57
8 and over	10	19	

Table II Age and sex

	Group I (cardiac rupture)	Group II (no cardiac rupture)	
Male	36 (66 yr 43-82)	35 (64 yr 39 86)	NS
Female	32 (73 yr 56-83)	33 (71 yr 47 89)	NS

Table III Location of the myocardial infarction (transmural)

	Group I	Group II	
Anterior	43 (63%)	36 (53%)	NS
Posterior	22 (31%)	20 (29%)	NS
Lateral	1 (1%)	3 (4%)	NS
Septal	2 (3%)	9 (14%)	NS

Table IV Location of the cardiac ruptures

Infarction	Free wall	Septum	Mixed
Anterior (43)	32	7	4
Lateral (1)	1	0	0
Posterior (22)	15	5	2
Septal (2)	0	2	0
Total cases	48	14	6

Mixed Septal and through the free wall

Table V Dimensions of the infarction

	Group I	Group II	
< 25%	11 (16%)	8 (12%)	NS
25 → 49%	48 (71%)	41 (60%)	NS
≥ 50%	9 (13%)	19 (28%)	NS
Connection ≤ 10 mm	60 (88%)	30 (44%)	p < 0 02

Connection Connection between necrosis and normal muscle

Table VI Older infarction and/or fibrosis

	Group I	Group II	
Old infarction	2 (3%)	24 (35%)	p < 0 001
Limited fibrosis	9 (13%)	8 (12%)	NS
Extent fibrosis	0	9 (13%)	p < 0 01

Table VII LVH and weight of the heart

	Group I	Group II	
LVH (mm)	14 43	14.51	NS
Weight (Gm)	411 (285 690)	457 (310-800)	p < 0 01

Table VIII Coronary arteries Stenosis and thrombosis

	Group I	Group II	
No stenosis	14 (21%)	5 (7%)	p < 0 05
One trunk	30 (44%)	11 (16%)	p < 0 03
Two trunks	16 (23%)	24 (36%)	NS
Three trunks	8 (12%)	28 (41%)	p < 0 03
Thrombosis	63 (93%)	54 (79%)	p < 0 05
Aorto-coronary bypass (possible)	27 (40%)	19 (28%)	NS

still numerous (see Table I) This complication is not related to the sex or age of the patient (see Table II)

The ruptures of the heart were unique in 59 cases (86 per cent) and multiple in nine cases (14 per cent) They occurred 48 times (70 per cent) through a free wall with related frequencies independent of the location of the myocardial necrosis (see Table III) The interventricular septum was the seat of the rupture 14 times (eight anterior six posterior i.e. 21 per cent) on which occasions it was more a case of ripping the connection between the septum and the adjacent free wall than a centroseptal perforation in six cases (9 per cent) the rupture was mixed (free wall and septum)

The rupture was situated in the zone of maximal myocardial destruction in 40 cases (59 per cent) it appeared at the center of the myocardial necrosis and at the periphery of the infarct in the other 28 cases (41 per cent) The internal aperture usually larger than its external extremity was in half of the cases hidden by mural thrombi the fistula was straight in a third of the cases otherwise irregular and jagged in three quarters of the observations it was associated

with intraparietal or blind ruptures which *amounted to a veritable dissection of the necrotic* muscle, the size of the external aperture varied from less than 1 sq cm in 22 cases (31 per cent), more than 1 sq cm in 46 cases (69 per cent) to a maximum of 80 mm in height (area, 5 sq cm) in one case

If the area of the myocardial infarct was found to be usually more limited in the case of cardiac rupture this information is not statistically significant (see Table IV) The transition from necrotic muscle to healthy tissue was effected in less than 10 mm in most cases of cardiac rupture ($p < 0.02$—see Table IV) An older myocardial infarct was exceptional in the case of cardiac rupture ($p < 0.001$) and so was the occurrence of widespread myocardial fibrosis ($p < 0.01$—see Table V) in both groups the incidence of left ventricular hypertrophy remained moderate although the mean weight of the heart was inferior ($p < 0.01$) in cases of cardiac rupture (see Table VI) The significant coronary stenoses were less frequent, less extensive and less widespread in the specimens showing a cardiac rupture (statistically significant datum) totally occlusive thromboses were the rule in group I ($p < 0.05$) the strictly anatomical possibilities of an aorto coronary bypass were more frequent in Group I though this did not prove statistically significant (see Table VII) yet the anatomical causes of impossibility were different a lower trunk most of the time normal but too narrow in the group with rupture and a greater distal extension of stenotic atherosclerosis in the other group (Table VIII)

Discussion

Cardiac ruptures through a free wall—the most frequent ones—can be a very early complication the same is true of septal perforations since their tell tale sign the systolic murmur, can be heard in almost half of the cases before the forty eighth hour

It is difficult to appreciate the exact frequency of heart ruptures 10,[8] 21,[9] to 24 per cent [10] The condition to obtain a totally accurate percentage would be for *all* recent fatal myocardial infarc tions to be followed by a postmortem examina tion

Absence of differences between the two groups As regards ruptures of the heart, London and London [11] Normand and associates, Wessler and associates[5] report a predominan occurrences among women This is not so where all that is noted is a greater age in wo moreover without relation to the presence absence of cardiac rupture

Those myocardial necroses susceptible leading to a rupture of the heart do not enj privileged location at the very most one c note that perforations of the septum are likely to be posterior than anterior, a fact alre reported by Gay [2] but without statistical sig cance When there is cardiac rupture the area of the necrotic zone represents about 3 per cent of the total area of the free walls of the ventricle and septum and 40 per cent (re infarctions) when there is *no* rupture a differe which is below the level of statistical significant though Naeim and associates[4] noted that sm size myocardial infarcts can be complicated ruptures as could indeed be seen in 16 per cen of the cases in this series

Differences between the two groups The heart is usually smaller in the case of cardi rupture (*$p < 0.01$*), *as* already observed by Cordeiro and associates[7] and Naeim and asso ciates [4]

Anatomical lesions *often* appear to be of different age a confirmation of the *observatio* of Cordeiro and associates[7] and Wessler a associates[5] in fact this seems to depend main on the extent of the infarct [13] The most usual finding is the extreme intensity of the myocardial necrosis in over two thirds of the *observation* least in and around the zone of *rupture*—to a dissection of the wall, a true necrotic mangling of the cardiac muscle This aspect, *also* reported by Cordeiro and associates[7] and Normand and asso ciates [9] is rarely observed in *the* absence of rupture of the heart The *transition* from healthy muscle to necrotic tissue usually takes a few millimeters in the case of cardiac rupture ($p < 0.02$) The extreme destruction *of* the myocardium in the necrotic zone *together* with the rapid transition from infarcted to healthy muscle are highly *suggestive* of the absence o impossible constitution of a substitutive circula tion from the other coronary trunks

An older myocardial infarct (however incom plete) and/or an older diffuse *myocardial fibro* are the exception in the case of cardiac rupture

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...ome researchers[4, 9, 15] register in the case of ...iac rupture an important and/or diffuse coro...y atherosclerosis In the present series signifi...t coronary stenosis are absent once in every ... cases ($p < 0.05$) when existing they are ...ricted to one trunk only in nearly half of the ...es ($p < 0.03$) and are short and proximal ...rly half the time As already reported by ...eim and associates[4] and Wessler and asso...tes[5] totally occlusive coronary thromboses are ...ctically always found in the case of cardiac ...pture ($p < 0.05$) whereas they are less frequent ... the control group[5, 6] Furthermore the domi...nt fact in this series is that in 21 per cent of the ...ses the coronary occlusion responsible for the ...yocardial infarction complicated by rupture is a ...rombosis in the absence of any atherosclerotic ...enosis superior to 50 per cent of the arterial ...men ($p < 0.05$)

Strictly anatomical study of the possibilities of ...rect myocardial revascularization does not ...ow any significant difference in the two groups ...et when it is not possible the causes are ...fferent in the case of cardiac rupture a usually ...ealthy artery below the occlusion though too ...arrow in the control group a distal extension ...f the atherosclerotic lesions This difference reaches the level of statistical significance

Summary

From an anatomical point of view the various elements which seem to individualize myocardial infarctions complicated by rupture are a limited increase in the volume of the heart a propensity for the rupture to follow the first infarction of a previously healthy cardiac muscle a myocardial necrosis of sometimes small extension with clear limits and a destruction of the muscle so severe as to amount in two thirds of the cases to a veritable parietal dissection a lesser extension and diffusion of coronary stenosis an ever present and totally occlusive coronary thrombosis an insignificant or absent substitutive circulation

Those *strictly anatomical facts* can be reason to extend the indications of a very early direct myocardial revascularization (almost a third of all cardiac ruptures occur within 24 hours) or to contemplate an infarctectomy after the eighth hour (the necroses are usually of a moderate size and well delimited) if it appears possible to draw the clinical profile of those patients prone to cardiac rupture or to read the signs that may announce the likelihood of this dreadful complication[16]

REFERENCES

1 Harvey W Quoted by Morgagni
2 Morgagni J B The seats and causes of disease London A Millar and T Cadell, lettre 27 vol 1
3 Cordeiro A Ravara L, Almeida M O and Cortao Clara J Les dilacerations myocardiques mortelles au cours de l infarctus aigu Arch Mal Coeur 66 1003 1973
4 Naeim F, de la Maza L M, and Robbins S L Cardiac rupture during myocardial infarction A review of 44 cases Circulation 45 1231 1972
5 Wessler S Zoll P M and Schlesinger M J The pathogenesis of spontaneous cardiac rupture Circulation 6 334 1952
6 Humbert J Rochemaure J and Lenegre J Les lésions anatomiques dans 100 anévrysmes ventriculaires après infarctus du myocarde Arch Mal Coeur 59 1?0? 1966
7 Deloche A Penther Ph, Humbert F, and Lenegre J Etude anatomo-radiologique de la revascularisation chirurgicale des infarctus du myocarde Arch Mal Coeur 66 59 1973
8 Maurice P Arnold E and Lenegre J Les ruptures du coeur par infarctus du myocarde Rev Atherosclerose 1 193 1959
9 Normand J Perrin A Plauchu G and Froment R Les ruptures pariétales et septales au cours des infarctus myocardiques Arch Mal Coeur 58 1311 1965
10 Spiekerman R E Brandenburg J T Achor R W, and Edwards, J E The spectrum of coronary heart disease in a community of 30 000 A clinipathologic study Circulation 25 57 1962
11 London R E and London S B Ruptures of the heart A critical analysis of 47 autopsy consecutive cases Circulation 31 202 1965
12 Gay J Les ruptures septales secondaires à un infarctus du myocarde Arch Mal Coeur 66 1513 1968
13 Leroy J P Schollhammer G Balouet G and Penther Ph. Influence de la duree d évolution et de la taille sur l aspect histologique de l infarctus du myocarde Arch Mal Coeur 68 4 9 19 5
14 Bjorck G Morgensen L Nyquist O Orinius E and Stogren A Studies of myocardial rupture with myocardial tamponade in acute myocardial infarction Chest 61 4 1972
15 Van Tassel R A and Edwards J E Rupture of heart complicating myocardial infarction Analysis of 40 cases including 9 examples of left ventricular false aneurysm Chest 61 104 1972
16 Haiat R Halphen C, and Chiche P Ruptures pariétales du coeur à la phase aigue de l infarctus myocardique Diagnostic précoce et approche thérapeutique actuelle Arch Mal Coeur 74 1457 1974

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uch a method to determine flow in the internal mammary is similar to the technique usually performed.[8]

Postoperative bypass flows were determined 2 weeks after surgery by angiographic methods described below. Of the 45 original patients undergoing saphenous vein bypass surgery to the left anterior descending artery, nine refused to be restudied and in one patient the graft was closed when studied. In the remaining 35 patients the saphenous vein graft was patent. However, in eight of these the angiographic study was not technically adequate for determining bypass flows by the method utilized. Six of these eight patients had studies with poor photographic results and the remaining two patients had overlaping opacified vessels adjacent to the distal portion of the graft. Because of these factors postoperative flows were not feasible by the method utilized. Of the 43 patients randomly selected for internal mammary artery bypass surgery five were eliminated from the study because of low intraoperative flows (≤ 50 ml per minute) in three and technical problems in isolating the internal mammary artery in two. It is generally recommended that intraoperative flows in the internal mammary artery of less than 50 ml. per minute are not suitable for utilizing as grafts. Five other patients who underwent internal mammary artery bypass surgery refused postoperative study. In two restudied patients the internal mammary artery graft was closed; in another six the angiographic study was not technically adequate for determining bypass flow by the method utilized. Therefore this study reports observations in 27 patients with saphenous vein and 25 with internal mammary artery bypass graft surgery to the left anterior descending artery.

Selective cineangiographic studies of the bypass graft to the left anterior descending artery were performed in a right anterior oblique projection at that angle indicating the long axis of the distal third of the graft to be parallel to the plane of the x ray table. Cineangiograms were taken with a 35 mm camera at 60 frames per second while 1 to 2 ml of 75 per cent sodium meglumine diatrizoate was injected over 1 second with a power injector (Vitamonte Hobbs). In all of the patients care was taken to insure that the catheter did not occlude the proximal orifice when performing the selective bypass angiogram. The catheter was also promptly withdrawn after the completion of the injection. Cine filming continued until all the contrast medium washed out of the graft. The x ray equipment included a dual field 6 inch 3 000 gain, 9 inch 6 000 gain image intensifier (General Electric) with a 35 mm (Photomechanism) synchronous camera utilizing a grid control x ray tube. When the selective cineangiogram was completed a grid of known dimension was positioned at the approximate location of the left ventricle and a short film strip taken to permit correction of errors due to magnification.

Blood flow in the bypass graft was determined by cinedensitometric methods similar in principle to those described by Rutishauser and co workers[1] and Smith and associates.[11] The determination of blood flow in saphenous vein bypass grafts by similar methods has previously been described. Cinedensitometric flow measurement is based on the derivation of a pair of indicator dilution curves from two separate points (S_1 and S_2) along the bypass graft. From two such curves the mean transit time between points S_1 and S_2 can be determined. When the distance between these two points and the mean diameter of the vessel is known the flow can be determined by the following equation

$$Q = \left\{\frac{d}{2}\right\}^2 \times \pi \times \frac{\Delta s}{\Delta t} \times 60$$

where Q = flow in milliliters per minute, d = mean graft diameter (in millimeters), Δs = distance (in millimeters) between S_1 and S_2, and Δt = mean transit time (in seconds) between the two points. This method does not require either knowledge of the amount of contrast medium injected or the concentration of contrast medium injected in the bypass graft in absolute units. However, the method is not valid if any vascular branches are present between the two indicator dilution points.

A Quantimet 720 image analyzing computer system (Imanco) incorporated with a Tagarno cine projector was utilized for recording the indicator dilution curves at two separate points in the distal third of the bypass graft. A high resolution vidicon camera using 720 line noninterlaced scan raster and a 10 6 frame per second scan rate optically coupled the densitometric system to the cine projector. Each scan line was digitized into

Comparative study of the postoperative flow in the saphenous vein and internal mammary artery bypass grafts

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Coronary artery revascularization is an accepted surgical approach for a select group of patients with symptomatic coronary artery disease The two types of grafts commonly utilized for coronary artery bypass are saphenous vein autografts[1] and the internal mammary artery[2] The advantages and disadvantages of the internal mammary artery bypass graft as compared to the saphenous vein, have been discussed by others[1-8] Comparative flow studies between the internal mammary artery and an autogenous vein used for coronary bypass have been investigated in the dog[3-5] No similar study has been reported in man The present study was designed to evaluate the postoperative coronary bypass flow in two groups of randomly selected patients receiving either autogenous saphenous vein or internal mammary artery bypass grafts to the left anterior descending artery

Methods

Any patient referred because of angina pectoris and considered on the basis of selective coronary angiography a surgical candidate for a revascularization procedure, was considered for the present study Selective coronary angiography had to demonstrate significant disease of the left anterior descending artery considered by the surgical team suitable for revascularization Only patients requiring a single or double bypass procedure were selected for this study On the basis of these requirements 88 patients were accepted a[illegible] randomly divided on the basis of the hosp[illegible] chart number into two groups One group of 4[illegible] patients was selected for a saphenous vein bypass graft, whereas the remaining 43 patients were selected for an internal mammary artery bypass graft to the left anterior descending artery Surgery, as previously described[8] was performed with total cardiopulmonary bypass cooling t[illegible] 32° and electrically induced fibrillation Intermittent aortic cross clamping and bulldog clamp control of the coronary arteries assured a dry field The left ventricle was continuously vented into the venous drainage via the right superior pulmonary vein Internal mammary pedicles when used were taken down prior to bypass Graft to coronary anastomoses were performed with one continuous suture and through a simple aortic incision over a partial occlusion clamp Intraoperative bypass flow in the saphenous vein graft was measured with a precalibrated electromagnetic flow probe (Statham Instruments Inc) Zero blood flow was obtained by clamping the graft just distal to the flow probe and adjusting the flowmeter All measurements were carried out in normothermia after the patient was off cardiopulmonary bypass and the blood pressure and heart rate stabilized Flow in the internal mammary artery was measured prior to cardiopulmonary bypass by permitting the transected end of the internal mammary artery to bleed into a graduated cylinder for 15 seconds

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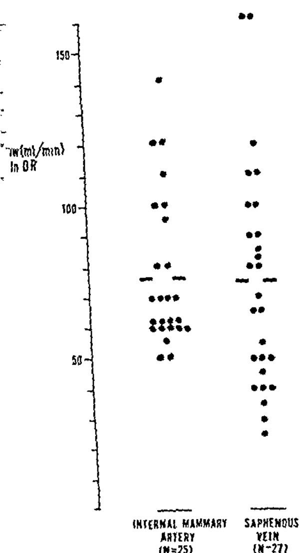


Fig 1 Intraoperative bypass flow for the individual patients in each group studied The horizontal bar is the mean for each group Flow in the internal mammary artery was determined by a time volumetric collection whereas flow in the saphenous vein graft was determined with a flowmeter (see Methods for details)

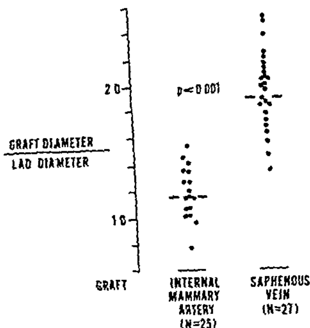


Fig 2 A comparison between the internal mammary artery group and the saphenous vein group of the relation of graft diameter to the diameter of the left anterior decending artery (LAD) A value above 1 indicates that the graft diameter is larger than the diameter of the LAD The horizontal bar is the mean value for each group

differences were noted between the groups for age duration of symptoms or frequency of hyper tension diabetes mellitus congestive heart failure transmural myocardial infarction or cardiomegaly Serum cholesterol and triglyceride revealed no group differences Intraoperative bypass flow studies were not significantly different when the two groups were compared (Fig 1) The mean intraoperative bypass flow in the SVG was 75 ± 27 ml per minute the mean flow at the time of surgery in the IMAG was 77 ± 24 ml per minute

At the time of postoperative angiographic study the heart rate and mean aortic pressure were 90 ± 16 beats per minute and 88 ± 7 mm Hg respectively in the SVG not significantly different from the IMAG where the heart rate was 90 ± 15 beats per minute and mean aortic pressure was 94 ± 14 mm Hg The mean graft diameters were 3 0 ± 0 5 and 1 9 ± 0 3 mm for the SVG and IMAG respectively ($p < 0\,001$) Relating the body surface area to the mean diameter of the internal mammary artery revealed a poor relationship ($R = 0\,45$ $p < 0\,025$) The ratio of the graft diameter to the left anterior descending artery diameter was 1 9 ± 0 3 and 1 2 ± 0 2 for the SVG and IMAG respectively ($p < 0\,001$) In 80 per cent of the patients with internal mammary artery grafts the ratio was less than 1 4 whereas in 89 per cent of the patients with saphenous vein bypass grafts the ratio was over 1 4 (Fig 2) Of note was the finding that almost 25 per cent (6/25) of the patients in the internal mammary artery group had a graft of a smaller diameter than the diameter of the left anterior descending artery (see Fig 2 graft dia/LAD dia < 1) Fig 3 demon

Table I Clinical profile of the two bypass groups

	Saphenous vein group	*Internal mammary artery group*
Number	27	25
Age (yr)	52 ± 11	55 ± 5
Body surface area (M^2)	1.88 ± 0.18	1.85 ± 0.12
Duration of symptoms (yr)	4.1 ± 3.1	3.7 ± 3.3
Hypertension (%)	29	28
Diabetes mellitus (%)	11	12
Congestive heart failure (%)	13	12
Cholesterol (mg/100 ml)	247 ± 61	230 ± 37
Triglyceride (mg/100 ml)	148 ± 47	160 ± 79
Myocardial infarction by ECG (%)	42	30
Enlarged heart on x ray (%)	17	20

Figures represent means ± 1 S D

approximately 1,000 picture points The video signal resulting from the scan of each cine frame coupled to a densitometer module permits the operator to adjust threshold of detection in order to select features in the video image for quantitation based on their density or gray level Setting the threshold for the detection of contrast medium is simplified by a real time system display capability in which the operator can observe the effect of varying the threshold level All video signals above the threshold level appear as an intensified overlay upon the original video image Variation in the light transmission of the image from cine frame to frame does not affect data accuracy which would normally result if the video signal varied about a fixed threshold An auto sensitivity circuit maintains a constant video signal output level from the scanner through a compensating effect on system gain Data from the densitometer is further controlled by a variable frame module Only detected features within the variable frame (or detecting window) are processed Horizontal and vertical dimensions of the variable frame (or window) are in picture points easily established by using a digi switch In the present study the variable frame or detecting window was 50 by 20 picture points where depending on the magnification factor one picture point was equivalent to 0.15 mm The position of the variable frame within the image area can likewise be controlled by a digi swi However, in order to automatically track th moving graft from cine frame to cine fra without operator control between two points S and S_2 on the bypass graft, a 9 830 HP softwar system (Hewlett Packard) was utilized Th system utilizes the area value to track the mov graft and keeps it centered within the frame (o window) boundaries established by the opera at the onset of the analysis The density value of the centered graft is determined at S_1 and S a stored in the software system which may later be transferred to magnetic tape for proces Following analysis of 'n cine frames two dil dilution curves from point S_1 and S_2 at a distanc ΔS are inscribed on an X Y plotter (Hewle Packard) simultaneously with the integral of each curve in order to determine the difference between the mean circulation time of the tw indicator dilution curves (Δt)

Prior to an actual run the mean vessel diameter (d) between points S_1 and S must be determined A variable frame (or window) of 100 to 200 pictur points high with a width adjusted to encompas the vessel width is positioned over the d al segment of the bypass graft, using a cine frame in which the bypass graft is fully outlined by contrast material The densitometer module is adjusted to outline at proper threshold settin the vessel encompassed by the variable frame The sum of all video picture points above the threshold and within the variable frame is automatically given as an area value and when divided by the height of the variable frame give the mean graft diameter in picture points Proper calibration converts picture points to millimeter In a similar manner for the purpose of this study the mean diameter of the left anterior descending artery adjacent to the graft anastamosis was determined

Results were expressed as the mean ± one standard deviation of the mean with statistical comparison between the saphenous vein bypass and internal mammary artery groups determined with the Student s unpaired t test

Results

The saphenous vein group (SVG) consisting of 27 patients was compared clinically with the patients in the internal mammary artery grou (IMAG) Table I displays various clinical parameters in the two groups of patients No significan

tients, graft closure was noted at the time of study, requiring reoperation and the use of a phenous vein graft Of great interest were three tients in whom the proximal portion of the ternal mammary artery demonstrated athero lerotic changes In one of these the atheromas mificantly compromised the wall lumen Fra r and co workers[13] have also observed athero lerotic involvement of the internal mammary rtery and commented that it may be more equent than previously implied These authors n the basis of their experience have recom ended preoperative and intraoperative evalua on of the internal mammary artery prior to its se as a bypass graft We concur with this and commend selective internal mammary arterio raphic studies at the time of the initial coronary ngiogram in any patient considered a candidate or internal mammary artery bypass surgery In ne patient not included in the present study a ft subclavian steal was present which was not inically apparent This negated the use of the ft internal mammary artery for coronary ypass surgery It was also evident that because f the tedious and time consuming dissection in isolating the internal mammary rtery such surgery could not be utilized in atients requiring prompt institution of cardio ulmonary bypass as in hypotension during nduction of anesthesia or emergency bypass urgery in the early stages of an acute myocardial nfarction

The roentgenographic indicator dilution tech uque for determining blood flow in the present tudy has been shown to be valid both in a model irculation as well as in vivo experiments when ompared to flowmeters [6] In vitro studies by is have shown that in tubes of the diameter omparable to saphenous veins there is an excel lent correlation for flows of less than 150 ml per minute Flows above 150 ml per minute tended to be underestimated by the angiographic method Determination of flow in a bypass graft to the left anterior descending artery is ideally suited for this method since the graft is an unbranched vessel and generally has a uniform diameter with a relatively straight distal portion Cinedensito metric determination of flow requires good quality cineangiography not only for deriving the indicator-dilution curves needed but for obtaining an accurate measurement of graft diameter

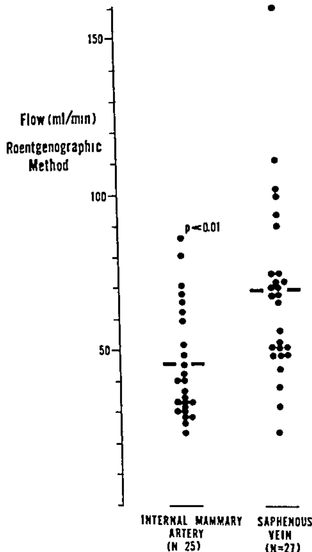


Fig 4 Bypass flow as determined postoperatively by roent genographic methods (see Methods for details) in each group studied. The horizontal bar is the mean for each group

When the diameter of various sizes of tubing filled with Hypaque was determined by the method utilized in this study there was excellent agree ment between the known diameters and the measured diameter Changes in graft diameter during systole and diastole although present were either of small magnitude or not perceptible One of the major problems with cinedensitom etric method is the influence of background density on the measurement of flow Contrast medium in a vessel over a high background density will show a different change in total field density as compared to a low background density

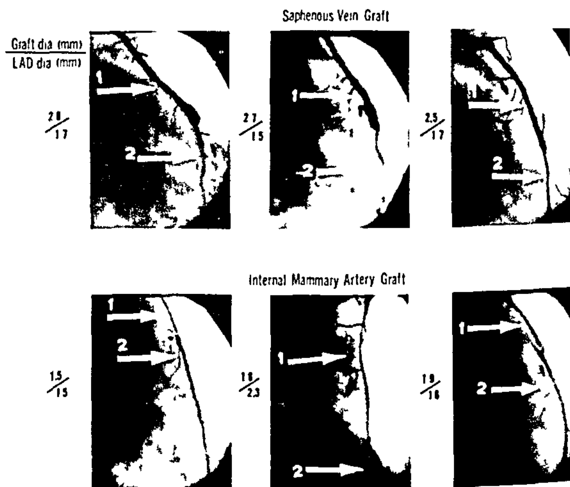


Fig 3 Selective angiograms of the patients with saphenous vein grafts to the LAD (upper) and three patients with IMA grafts to LAD (lower) The arrow labeled *1* points to the graft and the arrow labeled *2* points to the LAD The numbers to the left indicate graft diameter (numerator) and LAD diameter (denominator)

strates three typical cases from each of the groups studied, demonstrating the relationship of graft diameter to the diameter of the left anterior descending artery In three of the 25 patients in the IMAG, angiographic studies demonstrated atherosclerotic changes at the proximal portion of the internal mammary artery in one of whom the changes involved at least 50 per cent of the wall lumen

The postoperative flow as determined by roentgendensitometric methods was 68 ± 27 ml per minute in the SVG and 46 ± 16 ml per minute in the IMAG ($p < 0.01$) In 68 per cent of the patients with internal mammary artery grafts, the postoperative flow was 50 ml per minute or less, as compared with 33 per cent of the patients with saphenous vein grafts (Fig 4) As shown in Fig 5, in intraoperative flow for the IMAG, with but one exception overestimated the subsequently calculated roentgendensitometric flow determination whereas the comparison between intraoperative flow with the angiographically determined flow in the SVG revealed a wide scatter around the line of unity

Discussion

Although others[7,8] have presented the advantages in utilizing the internal mammary artery over the saphenous vein for bypass surgery several problems were evident in the small group of patients randomly selected for internal mammary artery surgery In the original 43 patients selected for internal mammary artery graft surgery, three had free flows at the time of surgery of less than 50 ml per minute Intraoperative flows of less than 50 ml per minute in the internal mammary artery are not recommended[2,8] as suitable for grafting Therefore in both of these patients a saphenous vein was utilized In two other patients, technical problems arose in isolating the artery necessitating the use of saphenous vein autografts In two

tients, graft closure was noted at the time of tudy requiring reoperation and the use of a phenous vein graft Of great interest were three tients in whom the proximal portion of the ernal mammary artery demonstrated athero erotic changes In one of these the atheromas nificantly compromised the wall lumen Fra r and co workers [3] have also observed athero lerotic involvement of the internal mammary tery and commented that it may be more quent than previously implied These authors the basis of their experience have recom ended preoperative and intraoperative evalua n of the internal mammary artery prior to its e as a bypass graft We concur with this and commend selective internal mammary arterio aphic studies at the time of the initial coronary giogram in any patient considered a candidate r internal mammary artery bypass surgery In e patient not included in the present study a t subclavian steal was present which was not nically apparent This negated the use of the t internal mammary artery for coronary bypass surgery It was also evident that because of the tedious and time consuming dissection required in isolating the internal mammary artery such surgery could not be utilized in patients requiring prompt institution of cardio pulmonary bypass as in hypotension during induction of anesthesia or emergency bypass surgery in the early stages of an acute myocardial infarction

The roentgenographic indicator dilution technique for determining blood flow in the present study has been shown to be valid both in a model circulation as well as in vivo experiments when compared to flowmeters In vitro studies by us have shown that in tubes of the diameter comparable to saphenous veins there is an excellent correlation for flows of less than 150 ml per minute Flows above 150 ml per minute tended to be underestimated by the angiographic method Determination of flow in a bypass graft to the left anterior descending artery is ideally suited for this method since the graft is an unbranched vessel and generally has a uniform diameter with a relatively straight distal portion Cinedensitometric determination of flow requires good quality cineangiography not only for deriving the indicator dilution curves needed but for obtaining an accurate measurement of graft diameter

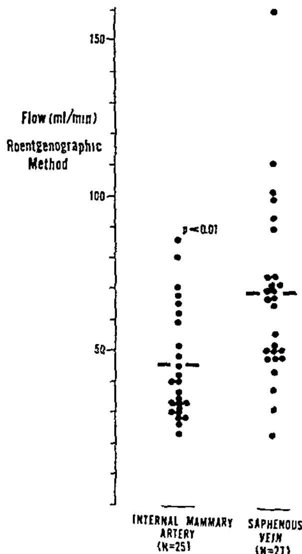


Fig 4 Bypass flow as determined postoperatively by roentgenographic methods (see Methods for details) in each group studied. The horizontal bar is the mean for each group

When the diameter of various sizes of tubing filled with Hypaque was determined by the method utilized in this study there was excellent agreement between the known diameters and the measured diameter Changes in graft diameter during systole and diastole although present were either of small magnitude or not perceptible One of the major problems with cinedensitometric method is the influence of background density on the measurement of flow Contrast medium in a vessel over a high background density will show a different change in total field density as compared to a low background density

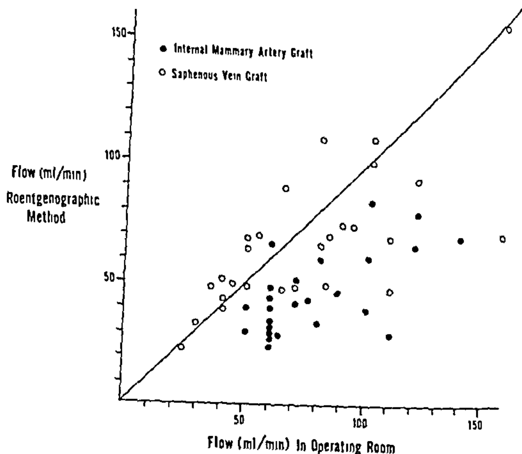


Fig 5 The relationship between *intraoperative* flow determination and postoperative roentgenographic flow determination for each patient in the groups of patients The straight line is the line of unity i e intraoperative flow equals postoperative roentgenographic flow Note in the saphenous vein bypass group a wide scatter around the line of unity whereas in the *IMA group* in *all* but one patient the points are below the line of unity

area Thus, uneven background density along the *course of a vessel will adversely affect the deter*mination of flow in that vessel Others have circumvented this problem by various methods[11] In the present study several cardiac cycles were observed before the graft was opacified and only those areas revealing equal background density were utilized *for flow* measurement Because of this limitation in 12 of 66 patients (18 per cent) flow studies were not *performed*, as it was not feasible to place the detecting window over two areas of the graft with *equal* background densities throughout the cardiac cycle Prior studies[11] demonstrated that the injection of contrast medium into the coronary artery may alter the coronary blood flow pattern Rutishauser and co workers[18] using small injectate volumes as in the present study, demonstrated good agreement for flow measured by roentgenographic technique in dogs when compared to electromagnetic flowmeter determination

The intraoperative flows in both the SVG and IMAG were comparable to those reported by others However the intraoperative *flow* in the internal mammary artery graft *reported* by Green[8] in his patients was considerably higher than in our group of patients *Such a difference* in flow may in part be explained by differences in technique and the use of papaverine *by Green* prior to recording flows There was a *random* relation between the intraoperative flows *and the* postoperative cinedensitometric flow studies in the group of patients with saphenous vein bypass grafts (Fig 5) This is *not an* unexpected finding since the physiological conditions (open chest anesthesia drugs) at the time of the *flow* studies were not comparable *However*, Fig 5 shows that for the group of patients with internal mammary artery grafts the postoperative cinedensitometric flows almost invariably underestimated the flows determined at the time of surgery The most reasonable *explanation for this finding* is the method used for measuring flow in the internal

ammary artery at the time of surgery Free aft flow measured by a timed volumetric llection just prior to making the anastomosis commonly utilized is a poor indicator of w after completion of the anastomosis since it presents flow taken with a negligible resistance the distal ostia and an infinite runoff Thus ch a flow determination would necessarily over timate the flow taken after the anastomosis nce in the latter situation the native coronary scular resistance and runoff would tend to duce the final flow For the two groups studied e mean differences between the intraoperative d postoperative flows were 7 and 31 ml per inute for the SVG and IMAG respectively

The difference in graft diameters between the vo groups studied was readily apparent (Fig 2 nd 3) In all the patients with saphenous vein e graft was always of larger diameter than the ft anterior descending artery In contrast in six 4 per cent) of the patients with internal ammary artery bypasses the graft diameter as less than the diameter of the left anterior escending artery It was found that the size of e internal mammary artery could not be redicted from the size of the patient At the time f the postoperative flow study there was no ifference in the mean aortic pres ure or heart ate for both groups of patients The significantly igher flow in the SVG as compared to the MAG may then possibly be due to the morpho ogical difference between the two types of grafts tilized The flow in the bypass graft is deter mined by the pressure gradient and vascular esistance across the entire vascular bed Since he graft is placed in series with the native oronary bed it will add to the total resistance of he vascular system as a direct result of its length and diameter The greater length and smaller diameter of the internal mammary artery will increase the total resistance to a greater extent than the saphenous veins Random selection of patients into two groups was necessary to elimi nate any influence of the native coronary circula tion as to vessel size and runoff A review of all the preoperative coronary angiograms in the patients studied revealed no differences in the mean diameter of the left anterior descending artery at the anastomotic site or qualitative evaluation of runoff when the two group of patients were compared Thus the lower flow in the internal mamary artery group may in part be due to the higher resistance it contributes to the vascular system than the wider saphenous vein grafts

Another possibility which may explain the higher flow in the saphenous vein grafts as compared to internal mammary artery grafts may be that proposed by Wakabayashi and co workers from observations made in dog experi ments These authors observed a higher flow in grafts originating in the ascending aorta than the internal mammary artery graft or a graft origi nating in the descending aorta In all three situa tions the mean arterial pressure at the origin of the grafts was similar whereas the mean diastolic pressures were significantly higher in the grafts originating from the ascending aorta and lowest in the internal mammary artery grafts The dias tolic pressure was sustained in the graft arising from the ascending aorta whereas at the orifice of the internal mammary artery a rapid rise and fall in the diastolic pressure occurs resulting in a higher mean diastolic pressure in the former and a lower mean diastolic pressure in the latter Thus the contour change in the pressure pulse as it is propagated along the aorta[11] may influence and determine the pressure gradient across the graft-coronary vascular bed Since the coronary flow occurs mainly during diastole the higher mean diastolic pressure in grafts originating from the ascending aorta would favor a higher flow as compared to the internal mammary artery graft An evaluation of the flow patterns in the grafts from the ascending aorta as compared to internal mammary artery grafts indicated that the differ ence in mean flow was due mainly to differences in diastolic flow

Morphological degenerative changes including intimal fibrous proliferation have been repeat edly described in saphenous vein grafts both experimentally[3] and clinically [ ] Such changes will in themselves compromise the wall lumen of the venous graft Thus the differences in saphe nous vein versus internal mammary artery flow noted in the early postoperative period may not be sustained after a longer follow up period In a small number of patients thus far followed this appears to be true in some cases However as already observed by us as well as Frazier and co workers the internal mammary artery is not immune to atherosclerotic changes especially at

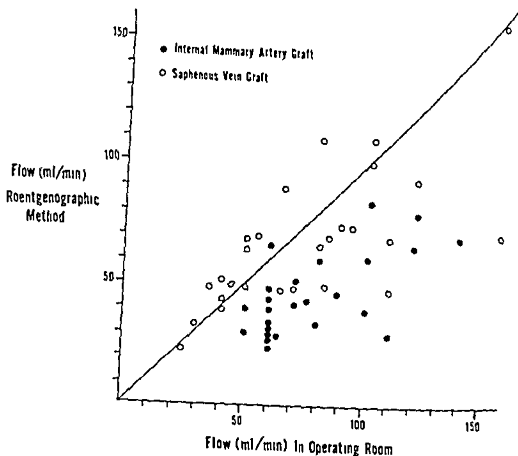


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results of vein bypass grafts for coronary artery disease Mayo Clin Proc 48 487 1973
Bainer H B Blood flow in the internal mammary artery Am Heart J 86 570 1973
Green G E Spencer F C Tice D A and Stertzer S H Arterial and venous microsurgical bypass grafts for coronary artery disease J Thorac Cardiovasc Surg 60 491 1970
Luchsinger P C Snell R E Patel D J and Fry D L. Instantaneous pressure distribution along the human aorta Circ Res. 15 503 1964
2 Grondin C M Meere C Castonguay Y., Lepage G and Grondin P Progressive and late obstruction of an aortocoronary venous bypass graft Circulation 43 698 1971
23 Vlodaver Z. and Edwards J F Pathologic changes in aortic coronary arterial saphenous vein grafts, Circulation 44 719 1971

its proximal portion Thus, the uncertainty about the long term fate of the grafts utilized for aorto coronary bypass surgery, as well as the inherent problems observed in the clinical applications of these grafts,[7, 8, 10] warrant reservations in making general recommendations for the adoption of one type of graft over the other

Summary

Postoperative coronary bypass flow was evaluated in two groups of randomly selected patients with grafts to the left anterior descending artery (LAD) Saphenous vein bypass grafts were placed in 27 patients and internal mammary artery grafts in 25 patients Postoperative flow studies were performed in both groups with roentgendensitometric methods based on the transit time of radiopaque media along the graft plus the mean graft diameter There was no significant difference between the two groups of patients for age duration of symptoms, or the frequency of hypertension, diabetes mellitus prior myocardial infarction or cardiomegaly Intraoperative bypass flows were 75 ± 27 and 77 ± 24 ml per minute for the saphenous vein group (SVG) and internal mammary artery group (IMAG) respectively There was no significant difference in the heart rate or mean aortic pressure at the time of the roentgendensitometric flow study The mean graft diameters were 3 0 ± 0 5 and 1 9 ± 0 3 mm for the SVG and IMAG respectively ($p < 0\ 001$) The ratios of graft diameter to LAD diameter were 1 9 ± 0 3 and 1 2 ± 0 2 for the SVG and IMAG respectively ($p < 0\ 001$) The roentgen densitometric postoperative flows were 68 ± 27 ml per minute in the SVG and 46 ± 16 ml per minute in the IMAG ($p < 0\ 01$) The present study indicates that flow in significantly higher in saphenous vein than in internal mammary artery bypasses and that the difference in flow may in part be explained on the basis of the graft diameter

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REFERENCES

1 Favaloro R G Effler D R Groves L K Sheldon W C and Riahi M Direct myocardial revascularization with saphenous vein autograft Clinical experience in 100 cases Dis Chest 56 279 1969

2 Green G E Internal mammary artery to coronary artery anastomosis Three year experience with patients Ann Thorac Surg 14 260 1972

3 Barner H B Kaiser G C Jellinek M Hahn, J W Amako H Ohtsubo M and Willman V L Aorto-coronary vein graft and internal mammary-coronary anastomosis Arch Surg 105 908 1972

4 Rossiter S J Brody W R Kosek J C Lipton, M and Angell W W Internal mammary artery versus autogenous vein for coronary artery bypass graft, Circulation 50 1236 1974

5 Hirose T and Marshall D A comparative study of the direct internal mammary-to coronary artery anastomosis and the aortocoronary vein bypass graft, Ann Thorac Surg 16 471 1973

6 Wakabayashi A Beron E Lou M A Mino J T Da Costa I A and Connolly J E Physiological basis for the systemic-to coronary artery bypass graft, Arch Surg 100 17 1970

7 Mills N L and Ochsner J L Technique of internal mammary-to coronary arterial bypass Ann Thorac Surg 17 237 1974

8 Green G E Rate of blood flow from the internal mammary artery Surgery 70 809 1971

9 Wisoff B G Hartstein M L Antablian A and Hamby R I Risk of coronary surgery Two hundred consecutive patients with no hospital deaths J Thorac Cardiovasc Surg 69 669 1975

10 Rutishauser W Simon H Stucky J P Schad N Nosida G and Wellauer J Evaluation of roentgen cinedensitometry for flow measurement in models and the intact circulation Circulation 36 951 1967

11 Smith H C Sturm R E and Wood E H Videodensitometric system for measurement of vessel blood flow particularly in the coronary arteries in man Am J Cardiol 32 144 1973

12 Smith H C Frye R L Davis G D Pluth J R Sturm R E and Wood E H Simultaneous indicator dilution curves at selected sites in the coronary circulation and determination of blood flow in coronary artery–saphenous vein grafts by roentgen videodensitometry in Heintzen P H editor Roentgen cine- and videodensitometry Fundamentals and applications for blood flow and heart volume determination Stuttgart 1971 Georg Thieme Verlag pp 159 157

13 Frazier B L Flemma R J Tector A J and Korns M E Atherosclerosis involving the internal mammary artery Ann Thorac Surg 18 305 1974

14 Bursch J Johs R Kirbach H Schnurer C and Heintzen P Accuracy of videodensitometric flow measurement in Heintzen P H editor Roentgen cine and videodensitometry Fundamental and applications for blood flow and heart volume determinations Stuttgart 1971 Georg Thieme Verlag pp 119 132

15 Guzman S V and West J W Cardiac effects of intracoronary artery injections of various roentgenographic contrast media Am Heart J 58 597 1960

16 Rutishauser W Bussman W Noseda G Meier W and Wellauer J Blood flow measurement through single coronary arteries by roentgen densitometry Part I A comparison of flow measured by a radiologic technique applicable in the intact organism and by electromagnetic flowmeter Am Heart J 109 12 1970

17 Grondin C M Miere C M Castonguay Y R Lepage G and Grondin P Blood flow through aorta to coronary artery bypass grafts and early postoperative patency A study of 100 patients Ann Thorac Surg 12 574 1971

18 Danielson G K Gau G T and Davis G B Early

Table I Dysfunction of the Bjork Shiley mitral disc prosthesis leading to the reoperation

Symptoms	Auscultatory findings	Time after the first operation (mo)	Cardiac catheterization	Emergency reoperation	Operative findings	Evolution	Cause of death
Sudden heart failure	Diminished opening clicks	8	Insufficiency and stenosis	Yes	Prosthesis thrombosis	Dead	O R death
Sudden heart failure	Systolic murmur	5	Insufficiency	No	Disc entrapment	Alive	–
Sudden heart failure	Systolic murmur	3	Not done	Yes	Leakage	Dead	O R death
Increasing cardiomegaly	Systolic murmur	24	Insufficiency	No	Leakage	Alive	–
Sudden heart failure	None		Not done	Yes	Prosthesis detachment	Dead	Low cardiac output
Sudden heart failure	Systodiastolic murmur	1	Insufficiency and stenosis	No	Disc entrapment	Alive	–
Dyspnea	Systolic murmur	5	Insufficiency	No	Leakage	Dead	Pneumonia
Hypotension oliguria coldness	None	Few hours	Not done	Yes	Technical error disc entrapment by suture	Dead	Pulmonary embolism?

O R = operating room

hospital whereas five were asymptomatic and followed a treatment with digitalis and acenocoumarin the other two patients had experienced no clinical improvement and were receiving the same treatment plus diuretics

Five of these seven patients were emergency admissions because of severe low cardiac output whereas two responded to medical treatment and were reoperated upon later three required immediate surgery because of a rapidly progressive clinical deterioration The two remaining patients underwent previous hemodynamic study because of either increasing cardiomegaly or symptomatic impairment (Table I)

Cardiac catheterization was performed on five of these seven patients and severe prosthesis dysfunction was demonstrated in all Three of the patients showed isolated valvular stenosis and two showed stenosis plus insufficiency The urgency for reoperation did not permit catheterization in one patient in one other patient we considered *catheterization* unnecessary since abnormal prosthesis movement was clearly observed by fluoroscopy

Operative findings

In one patient whose anticoagulant treatment had been interrupted by his doctor 1 month earlier for unknown reasons a massive thrombus that covered both sides of the valve and almost completely immobilized the disc was found The valve was replaced with a similar Bjork Shiley prosthesis

In another patient the valve was found almost completely detached (in fact only one suture remained intact) and endocarditic vegetations affecting both the mitral annulus and the prosthesis were seen After the first operation this patient had developed fever and had experienced no symptomatic improvement but repeated blood cultures had been negative and no other signs of endocarditis had appeared Despite the fact that cultures of the vegetations and of the prosthesis were negative we attributed the detachment to infection

Three other patients had paravalvular leakage in one case four leaks were corrected by new sutures supported on Teflon in the other two patients the prostheses were replaced because of extensive detachment A pannus on the ring which did not interfere with disc function was observed in one of the latter

In two patients the prostheses appeared normal seen from the atrial side being free of any foreign matter and with all the sutures intact On moving the discs however we discovered that they struck thick bands of muscle on either the interventricular septum or the left ventricle wall orientation of the larger valve orifice was anterior in the first case and posterior in the second Both of these patients had received the largest sized valve (No 31) In both cases the prostheses were

Reoperation for dysfunction of the Björk-Shiley mitral disc prosthesis

REPORT OF EIGHT CASES

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It is well known that few failures are generally reported during the first years a new prosthetic device is used, and that over a period of time, and with their more generalized usage, problems seemingly inherent to every heart valve prosthesis (thrombosis infection, leakage),[1] as well as various mechanical failures related to the materials employed and the particular valve design tend to appear

Up to date, few failures requiring replacement of Björk Shiley prostheses have been described We present our experience of eight cases requiring substitution of Björk Shiley mitral prostheses because of valve dysfunction

Materials and methods

During the period between March 1971, and December 1974, we have implanted 193 Björk Shiley mitral prostheses in the Clinica Puerta de Hierro (143 isolated mitral valve replacements and 50 multiple valve replacements) In eight patients (4 1 per cent) all with isolated mitral prostheses replacement was required because of valve dysfunction Four of the patients were male and four were female with ages ranging from 32 to 49 years (average 37 3 years) Their clinical records were reviewed and constitute the subject of this work

While some of the first prostheses were implanted with a continuous suture the remaining prostheses were fixed with approximately [illegible] single Ethiflex sutures in the subannular position with the use of the technique described by Björk and associates Most of the prostheses were oriented with the larger orifice facing anteriorly and once in position, valve function was checked and free disc movement was assured

Prosthesis failures

One of the patients developed hypotension oliguria and skin coldness with profuse sweating within a few hours after leaving the operating room This condition did not improve with medical treatment on reoperation we discovered one suture crossing the ventricular surface of the disc that almost totally impeded its opening The prosthesis was replaced with a similar one and the postoperative course was uneventful up to the fourth day when cyanosis and dyspnea appeared suddenly and the patient suffered a cardiac arrest which did not respond to any recovery manipulation The clinical diagnosis was pulmonary embolism but permission for autopsy was not obtained

The other seven patients were reoperated upon between 2 and 24 months after the initial valve replacement All had been discharged from the

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-earance of this complication it is highly -able however that the placement of the theses in the subannular position contributed ts presentation

Two subgroups can be made in regard to death h the seven patients discharged from the pital after the first operation one group of -e patients admitted with low cardiac output l shock and who required urgent operation l another group of four patients that received tive surgery All the patients in the first group d either in the operating room or within a few urs after surgery while only one patient of the ond group died and this death was not of a ect cardiac origin but consequent to respira y insufficiency and sepsis secondary to pneu -nia It is obvious that an early diagnosis of tral prosthesis dysfunction by catheterization -uld reduce the number of patients requiring -ergency surgery

Urgent operation seems justified with or -thout prior catheterization whenever symp -ms begin suddenly and a patient reaches the -spital with severe heart failure if the suspicion prosthesis dysfunction exists Bjork and asso -ites[11] recommend immediate surgery without -ior catheterization whenever aortic prosthesis -sfunction is suspected in patients with severe -v cardiac output

The evaluation of mitral prosthesis dysfunction more difficult Our data suggest that if postop -rative functional improvement does not occur -modynamic studies should be performed as -arly as possible in an attempt to discover the -robable cau e of failure This would permit the -dentification of cases of prosthesis dysfunction -hich might otherwise be attributed to an altera -on of cardiac performance

In the same sense whenever a patient s status -eteriorates rapidly prosthesis dysfunction -hould always be considered a possibility Auscul -atory findings have been deceptive and in some -ases the combined use of such noninvasive -methods as fluoroscopy phonocardiogra -phy and echocardiography may provide -enough evidence to indicate surgical exploration We believe however that diagnostic procedures -hould not unnecessarily delay reoperation since our results suggest that if surgery is performed before the patient enters shock the prognosis may be acceptable

Summary

Of 193 patients with Bjork Shiley mitral valve prostheses replacement was necessary in 8 (4 1 per cent) The reasons for reoperation were detachment (4) thrombosis (1) technical error (1) and late disc entrapment (2) Five of these patients died (62 5 per cent) the death being directly related to the need for urgent operation because of low cardiac output We recommend avoiding the use of the larger sized Bjork Shiley prostheses since striking of the disc against the ventricle wall probably consequent to postopera tive decrease in heart size may appear even 1 year after implantation of the prostheses

An early diagnosis and early reoperation offer these patients a much more favorable prognosis

Addendum

Since the submission of this manuscript we have operated on another case of a thrombosed Bjork Shiley mitral prosthesis in a patient who had discontinued anticoagulation therapy per forming a simple thrombectomy The patient s recovery was uneventful

REFERENCES

1. Herr R H Starr A McCord C et al Special problems following valve replacement Embolus infection red cell damage leak, Ann Thorac Surg 1 403 1965
2. Bjork V O Book K and Holmgren A The Bjork Shiley mitral valve prosthesis A comparative study with different prosthesis orientations Ann Thorac Surg 18 3 9 1974
3. Lansing A M Unusual radiologic sign of loose mitral valve prosthesis Radiology 88 789 1967
4. Bjork L and Bjork V O Cineradiography in the postoperative control of a Starr aortic valve prosthesis Thorax 21 48 1966
5. Stinson E B Castellino R A and Shumway N E Radiologic signs in endocarditis following prosthetic valve replacement J Thorac Cardiovasc Surg 56 554, 1968
6. Kastor J A Akbarian M Buckley M J et al Paravalvular leaks and hemolytic anemia following insertion of Starr Edwards aortic and mitral valves J Thorac Cardiovasc Surg 56 9 9 1968
7. Ben Zvi, J Hildner F J Chandraratna P A et al Thrombosis on Bjork Shiley aortic valve prosthesis Clinical arteriographic echocardiographic and therapeutic observations in 7 cases Am J Cardiol 34 538 19 4
8. Cokkinos D V Voridis E Bakoulas G et al Thrombosis of two high flow prosthetic valves J Thorac Cardiovasc Surg 62 947 1971
9. Bjork V O Henze A and Holmgren A Five years experience with the Bjork Shiley tilting-disc valve in isolated aortic valvular disease J Thorac Cardiovasc Surg 68 393 1974
10. Messmer B J Okies J E Hallman G L et al Aortic

replaced with similar valves of a smaller size, obtaining free disc movement

The one patient requiring reoperation during the immediate postoperative period has already been described

Clinical evolution

Five of the eight patients died in the hospital (62 5 per cent) One death has already been described two patients could not be taken off cardiopulmonary bypass (one had suffered three cardiac arrests before the thorax was opened), and one other patient died several hours after reoperation of severe low cardiac output These last three patients who died either in the operating room or shortly after surgery, were all operated on an emergency basis because of a rapid clinical deterioration

The fifth patient died of pneumonia with sepsis and respiratory insufficiency on postoperative day 27

The three surviving patients were all asymptomatic at 3 16 and 36 months after surgery

Discussion

Up to the present time few complications causing death or requiring replacement because of Bjork Shiley prosthesis dysfunction have been described The majority have been complications common to all artificial heart valves (thrombosis and leakage) [11] Mechanical failure has been described in two patients in whom disc dislodgment of either a mitral or an aortic prosthesis occurred[15, 16] in one case dislodgment was attributed to mishandling of the prosthesis [5] Considering that the Bjork Shiley prosthesis has been in use for 7 years, we feel that the incidence of complications reported has been small

Of the 193 Bjork Shiley mitral prostheses implanted by our group during a period of almost 4 years 8 (4 1 per cent) developed severe dysfunction that required replacement We feel that this high incidence can be reduced with better operative technique and with more experience with the valve itself Since September 1973 only one of 73 mitral prostheses implanted by us has required replacement

One case of prosthesis dysfunction was due to a purely technical error, and the patient was reoperated upon within a few hours after the initial operation one of the sutures used for securing the prosthesis crossed under its ve[illegible] ular surface and prevented its complete ope[illegible] Bednarik and associates[17] have reported a s[illegible] case occurring with a Starr Edwards aortic p[illegible] thesis Since our incident, we always check p[illegible] thesis function once in place before tying t[illegible] sutures and in one case of aortic valve re[illegible] ment, we discovered and corrected a s[illegible] error

The most common cause of valve dysfu[illegible] in our series was detachment of the prosth[illegible] (four cases) Messmer and associates[11] descr[illegible] six cases of detachment of Bjork Shiley m[illegible] prostheses (one associated with thromb[illegible] requiring reoperation in a series of 108 patients [illegible] this group, continuous sutures were ini[illegible] employed in securing the valves Bjork and a[illegible] ciates reported only two cases requiring reoper[illegible] tion because of leakage in a series of 200 m[illegible] valve replacements While paravalvular [illegible] leaks are more frequently associated [illegible] calcified valves this relation seems to be [illegible] important in mitral replacements where det[illegible] ment has been frequently related to a pos[illegible] defect of the connective tissue of the valve an[illegible] lus [6] Of our four patients with prosthesis det[illegible] ment one had a severely calcified mitral val[illegible] one had an almost complete detachment wh[illegible] we attributed to endocarditis, and in another t[illegible] prosthesis had been secured with a continu[illegible] suture In the fourth patient no justification [illegible] detachment was found

In the two patients who had received t[illegible] largest sized prosthesis (No 31), dysfunction was caused by disc entrapment against either the interventricular septum or the ventricle wall appearing at 5 and 12 months after the initial replacement It is highly probable that the decrease in the size of the heart chambers after hemodynamic correction created a problem of space which interfered with prosthesis functio[illegible] Several cases of late dysfunction of mitral ball valves[1] and caged disc prostheses[21] attributed to a large prosthesis size in relation to a small ventricle have been reported Our two cases of disc entrapment (both long term) are the first to be described occurring with a tilting disc prosthesis and they could have easily been avoided by using a smaller sized valve Given the fact that the disc orientation was different in both cases we doubt that this factor contributed to the

senmenger s syndrome ın pregnancy

ıes heparın prophylaxıs ımprove the maternal mortalıty rate?

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ısenmenger s syndrome ıs defined as pulmonary ypertensıon with a reversed or bidirectional hunt at the aorta pulmonary ventricular or trıal level Earlier reports suggest that this ısease ıs associated with a high maternal ıortality rate ın late pregnancy and particularly ı the puerperium [1] supposedly through pulmonary arterial occlusion Prophylactic heparin herapy in the puerperal period has been recomrended as a means to help these patients through ırevention of pulmonary thromboembolism [2] The ıurpose of this review of seven cases ıs to examine whether anticoagulation and careful monitoring of the patient ın an intensive care unit ın the postpartum or postoperative period improves the morbidity and mortality rates of the Eisenmenger syndrome ın relation to pregnancy

Case descriptions

Between 1962 and 1974 seven women with Eisenmenger s syndrome were seen ın the Women s Clinic at the University of Oklahoma Health Sciences Center Six of the patients presented between eight and 31 weeks of pregnancy and one nulliparous nonpregnant patient presented for tubal ligation All patients had undergone cardiac catheterization prior to pregnancy and the diagnosis of Eisenmenger s syndrome was established ın each Criteria for clinical diagnosis of Eisenmenger s syndrome were cyanosis and clubbing of the fingernails loud pulmonary component of the second heart sound on auscultation and right ventricular hypertrophy on the chest film and electrocardiogram In each case cardiac catheterization had demonstrated equal pulmonary arterial and aortic pressures with a predominantly right to left shunt The hemodynamic findings ın our seven patients are shown ın Table I

Case 1 M S 25 years of age presented during the thirtieth week of her first pregnancy She had had cyanosis of the digits since infancy A cardiac catheterization had been performed at age 15 because of frequent respiratory infections moderate exercise intolerance and substernal chest pain The patient was hospitalized at 32 weeks of gestation because of ankle edema At 36 weeks of gestation labor was induced and the patient delivered a term infant under saddle block anesthesia The patient was then transferred to the intensive-care area for monitoring. Intravenous heparin 5 000 units every 4 hours was begun immediately after delivery but heparin was discontinued 48 hours later because of excessive vaginal bleeding The patient became hypotensive and blood transfusion was given. On the sixth postpartum day the patient had a sudden drop in blood pressure followed by a grand mal seizure and death. At autopsy the right ventricle was hypertrophied. There was a 3 cm. interventricular septal defect and a 2 mm patent ductus arteriosus There were several atherosclerotic plaques ın the intima of the pulmonary artery as well as intimal and medial hyperplasia ın the medium sized and small pulmonary arteries (Fig 1) The lungs were edematous without evidence of infarction and there was an infiltrate ın the left lower lobe

Case 2 E S was known to have had heart disease since early childhood manifested by cyanosis on exercise and by frequent respiratory infections At age 27 a hemodynamic and angiographic evaluation was performed The patient became pregnant the following year During the fifth month of pregnancy the patient was hospitalized briefly because of false labor At the expected date of confinement the patient

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valve replacement Two years *experience* with the Bjork Shiley tilting disc prosthesis Surgery **72** 772 1972
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12 Lepley P Discussion of Bjork et al Ann Thorac Surg **18** 386 1974
13 Concha P Discussion of Bjork and associates Ann Thorac Surg **18** 389 1974
14 Messmer B J Okies J F Hallman C L et al Mitral valve replacement with the Bjork Shiley tilting disc prosthesis J Thorac Cardiovasc Surg **62** 938 1971
15 Messmer B J Rothlin M and Senning A Early disc dislodgment An unusual complication after insertion of a Bjork Shiley mitral valve prosthesis J Thorac Cardiovasc Surg **65** 386 1973
16 Mulder G A Discussion of Bjork and associates J Thorac Cardiovasc Surg **68** 403 1974
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18 Joassin A and Edwards J E Late causes of death after mitral valve replacement Analysis of 36 cases J Thorac Cardiovasc Surg **65** 255 1973
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20 Glancy D L O Brien K P Reiss R L et al Hemodynamic studies in patients with 2M and 3M Edwards prosthesis Evidence of obstruction to left [illegible] emptying Circulation **39 40**(Suppl. I) 113, 1969
21 Roberts W C Fishbein M C and Golden A Cardiac pathology after valve replacement by disc prosthesis [illegible] study of 61 necropsy patients, Am J Cardiol **35** 1975
22 Keen G Late death due to escape of ball from [illegible] valve prosthesis J Thorac Cardiovasc Surg **67** 1974
23 Leachman R D and Cokkinos D V P Absence of opening click in dehiscence of mitral valve prosthesis [illegible] Engl J Med **281** 461 1969
24 Crage F Hutchin P and Sutton R Impaired function of cloth covered Starr Edward mitral valve prosthesis Detection by phonocardiography Circ **41** 141 1970
25 Pfeiffer J Goldschlager N Sweatman T et al Malfunction of mitral ball valve prosthesis due to thrombus Report of two cases with notes on early diagnosis Am J Cardiol **29** 95 197[illegible]
26 Douglas J F and Williams G D Echocardiographic evaluation of the Bjork Shiley prosthetic valve Circulation **50** 52 1974

enmenger s syndrome in pregnancy

's heparin prophylaxis improve the maternal mortality rate?

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senmenger s syndrome is defined as pulmonary pertension with a reversed or bidirectional unt at the aorta pulmonary ventricular or rial level[1] Earlier reports suggest that this sease is associated with a high maternal ortality rate in late pregnancy and particularly the puerperium[2,3] supposedly through pul onary arterial occlusion Prophylactic heparin ierapy in the puerperal period has been recom iended as a means to help these patients through revention of pulmonary thromboembolism[3] The urpose of this review of seven cases is to examine whether anticoagulation and careful monitoring f the patient in an intensive care unit in the postpartum or postoperative period improves the norbidity and mortality rates of the Eisenmenger syndrome in relation to pregnancy

Case descriptions

Between 1962 and 1974 seven women with Eisenmenger s syndrome were seen in the Women s Clinic at the University of Oklahoma Health Sciences Center Six of the patients pre sented between eight and 31 weeks of pregnancy and one nulliparous nonpregnant patient pre sented for tubal ligation All patients had under gone cardiac catheterization prior to pregnancy and the diagnosis of Eisenmenger's syndrome was established in each. Criteria for clinical diagnosis of Eisenmenger's syndrome were cyanosis and clubbing of the fingernails loud pulmonary component of the second heart sound on auscul tation and right ventricular hypertrophy on the chest film and electrocardiogram In each case cardiac catheterization had demonstrated equal pulmonary arterial and aortic pressures with a predominantly right to left shunt The hemody namic findings in our seven patients are shown in Table I

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18 Joassin A and Edwards J E Late causes of death after mitral valve *replacement Analysis of 36* cases J Thorac Cardiovasc Surg **65** 255 1973
19 Shepherd R L Glancy D L Stinson E B et al Hemodynamic confirmation of the obstruction to ventricular inflow by a caged ball prosthe[illegible] valve J Thorac Cardiovasc Surg **65** 2[illegible] 1973
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22 Keen G Late death due to escape of ball from [illegible] valve prosthesis J Thorac Cardiovasc Surg 67[illegible] 1974
23 Leachman R D and Cokkinos D V P Abs[illegible] opening click in dehiscence of mitral valve prosth[illegible] Engl J Med **281** 461 1969
24 Craige E Hutchin P and Sutton R Impaired [illegible]tion of cloth covered Starr Edwards mitral valve pr[illegible]thesis Detection by phonocardiography Circ[illegible] **41** 141 1970
25 Pfeiffer J Goldschlager N Sweatman T [illegible] Malfunction of mitral ball valve prosthesis due to th[illegible]bus Report of two cases with notes on early [illegible] diagnosis Am J Cardiol **29** 95 1972
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Fig 2 Histologic section of a small muscular pulmonary artery and its branches from patient E S There is complete obliteration of the lumen with early evidence of recanalization

deeply cyanotic Pulmonary artery thrombosis was suspected but the patient died before pulmonary angiography could be performed. Autopsy permission was refused

Case 5 C E had had symptoms of breathlessness and easy fatigability since early childhood Cardiac catheterization was performed at age 11 which showed a ventricular septal defect and pulmonary artery pressure equal to systemic pressure The ventricular septal defect was corrected surgically and an interatrial slit was created at operation The patient's symptoms persisted after surgery The patient became pregnant at the age of 19 Therapeutic abortion was refused by the patient Her symptoms began to worsen during the twenty third week of pregnancy During the twenty fifth week the patient was hospitalized for hemoptysis and dyspnea at rest The hospital course was marked by recurrent hemoptysis increasing cyanosis and attacks of loss of consciousness The patient was transferred to the intensive-care area where therapy with 100 per cent oxygen and anticoagulation with 5 000 units of heparin every 4 hours was instituted with some symptomatic improvement during the following 72 hours On the seventh hospital day dyspnea and cyanosis increased simultaneously with the onset of severe right sided chest pain Pulmonary infarction was suspected The patient became progressively hypoxic and died 24 hours later Autopsy permission was refused.

Case 6 L B 21 years of age was known to have had a ventricular septal defect and pulmonary hypertension since the age of 5 The patient was hospitalized for tubal ligation and therapeutic abortion during the fifteenth week of pregnancy An abdominal tubal ligation was performed under a local anesthetic without complications The following day 40 mg of prostaglandin F were infused into the amniotic sac Abortion occurred 10 hours later Eight hours after abortion the patient developed mild right sided heart failure and increasing hypoxia She improved gradually with catecholamine infusion and 100 per cent oxygen therapy The patient was discharged to her home from the intensive-care unit on the eleventh hospital day She has been without further complications

Case 7 D W had had dyspnea on moderate exertion and cyanosis at rest since childhood. Because of marked limitation of exercise tolerance cardiac catheterization was performed at the age of 14 The patient was seen again at age 18 for therapeutic abortion at 12 weeks of pregnancy The patient aborted spontaneously several hours after hospitalization Four years later she died during induction of anesthesia for a major surgical procedure Reportedly there were no other pregnancies. Autopsy permission was refused

Discussion

It is clear from these cases and others in the literature that patients with Eisenmenger's syndrome withstand pregnancy and surgical procedures poorly[2, 3] The maternal mortality rate in reported cases including these may be established between 30 70%[3] This is in contrast to the low maternal mortality rate during pregnancy in congenital defects not associated with pulmonary hypertension and shunt reversal[5, 6] Prophylactic heparin in therapeutic doses was of no value in preventing deterioration in five of our patients and may have contributed to the death of three of them by inducing excessive bleeding and hypotension In the five fatal cases monitoring in the intensive care unit did not prevent sudden death



Fig 1 Histologic section of a small muscular pulmonary artery from patient M S Note the almost complete obliteration of the lumen due to medial hypertrophy and intimal hyperplasia

Table 1 Hemodynamic data

Patient	*Age at diagnosis*	*Mean pul art pressure*	*Arterial oxygen saturation (%)*	*Anomaly*
M S	1 6/12	84	84	VSD + PDA
E S	27	81	87 5	VSD + partial transposition
J G	17	96	82	VSD + partial transposition
C S J	17	93	84	VSD
C E	11	73	96	VSD
L B	5	70	95	VSD
D W	6	Equal to systemic	89	VSD + anomalous venous return and dextrocardia

delivered a 2 100 gram infant under low spinal anesthesia supplemented with ether and oxygen After delivery intravenous heparin 5 000 units every 4 hours was begun in the intensive care unit The patient did well until the fifth postpartum day when she developed congestive heart failure and a urinary tract infection Digitalis and antibiotics were started The following afternoon the patient developed sudden severe respiratory distress followed an hour later by respiratory and cardiac arrest that was refractory to all resuscitative measures At autopsy there was a large right ventricle an interventricular septal defect and dextroposition of the aorta The main pulmonary arteries showed extensive atherosclerotic plaques without occlusion The smaller pulmonary arteries exhibited hyalinization of the media and generalized hyperplasia of the intima with revascularization of the lumen (Fig 2) Alveolar hemorrhage and bilateral pleural effusions were also noted

Case 3 J G presented at 17 years of age with complaint of dyspnea on mild exertion She had not been pregnant. Because of the hemodynamic findings pregnancy was felt to be contraindicated One year later the patient underwent a vaginal tubal ligation under spinal anesthesia In the immediate postoperative period the patient became hypotensive she developed both direct and rebound abdominal tenderness and the hematocrit value dropped significantly over the next hours. An exploratory laparotomy was performed under a general anesthetic At operation a vessel to the right Fallopian tube was ligated and 1 800 c c of blood were found in the peritoneal cavity Blood loss was replenished and the patient remained stable in the intensive care unit until the third postoperative day when she developed tachycardia chest pain fever and marked increase in cyanosis Pulmonary artery occlusion was suspected and intravenous heparin 5 000 units every 4 hours was instituted During the following 36 hours the patient became progressively hypoxic and acidotic and died in cardiac asystole Autopsy permission was refused

Case 4 C S 19 years of age presented in the thirty fifth week of pregnancy She had been known to have heart disease with finger clubbing cyanosis and moderate exercise intolerance since early childhood Cardiac catheterization at age 17 confirmed the diagnosis of Eisenmenger s syndrome Labor was induced in the thirty ninth week of pregnancy the patient delivered a normal infant and heparin therapy was started immediately after delivery The patient developed fever and suffered a tonic clonic seizure on the second postpartum day Antibiotics were begun after appropriate blood cultures were taken Profuse vaginal bleeding occurred on the third postpartum day Heparin was discontinued and the patient was transfused with 4 000 ml of whole blood On the fifth postpartum day the patient became severely short of breath

e also could have adverse effects by inducing
)ventilation This was clearly demonstrated
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s to 38 units with sedation The rapid deteri
ion in patient L B following intraamniotic
tion of prostaglandin F_2 to induce abortion
· be attributable to the bronchoconstricting
pulmonary vasoconstricting effects of that
[18] The steady improvement seen in this
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v and decreased right to left shunting Alveo
hemorrhage as seen with the clinical deterio
ion of patient E S has been shown to occur
nmonly in patients with Eisenmenger s syn
ome and could have been contributed to by
poxia and heparin therapy

Continuous monitoring in the intensive care
it was of no benefit in preventing or reversing
deterioration seen in five of our patients It
uld seem that prompt attention to blood loss
potension or infections did little to alter the
tcome in these cases

We feel that pregnancy should be strongly
lvised against in patients with Eisenmenger s
ndrome The known relationship between oral
ontraceptives and venous thromboembolism
akes the use of these drugs potentially hazard
is in these patients Sterilization by tubal liga
on or fulguration preferably under local anes
iesia is the method of choice in preventing
regnancy in patients with Eisenmenger s syn
rome in the child bearing age

Summary

Seven consecutive patients with Eisenmenger s yndrome cared for by the obstetric team in onjunction with the cardiology service were eviewed to assess the possible role of prophy actic heparin therapy and intensive care on the outcome of these patients In each patient the diagnosis of Eisenmenger s syndrome was estab ished by the demonstration of equal pulmonary arterial and aortic pressures with a predomi nantly right to left shunt at cardiac catheteriza tion

Five of the seven patients died as follows Three patients died between the fifth and eighth post partum days one patient died during the twenty sixth week of pregnancy and one patient died on the fifth postoperative day following tubal liga tion All of these five patients received prophy lactic heparin therapy In three patients heparin therapy was complicated by excessive bleeding during the postoperative or postpartum period Autopsy examination in two patients revealed no evidence of thrombosis in the main pulmonary arteries and no pulmonary infarction contrary to the antemortem clinical suspicion

The two survivors did not receive prophylactic heparin They comprised one patient who had normal delivery and one patient who underwent tubal ligation and induction of abortion

We conclude that the prohibitive mortality rate of Eisenmenger s syndrome during preg nancy puerpurium or surgical procedures proba bly cannot be modified with prophylactic heparin therapy Anticoagulant treatment does not prevent deterioration of patients and probably compounds the problem by causing significant bleeding

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REFERENCES

1 Wood, P Pulmonary hypertension Br Med Bull. 8 348 1952
2 Neilson G Galea E G and Blunt A Eisenmenger syndrome in pregnancy Med J Aust 1 431 1971
3 Jones A M and Howeth G Eisenmenger syndrome in pregnancy Br Med. J 2 1627 1965
4 O'Neal, R M and Thomas, W A The role of pulmonary hypertension and thromboembolism in the production of pulmonary arteriosclerosis Circulation 12 370 1955
5 Neilson G Galea E G and Blunt A Congenital heart disease and pregnancy Med. J Aust 1 1086 1970
6 Conradsson T B and Werko L Management of heart disease in pregnancy Prog Cardiovasc Dis 46 407 1974
7 Metcalfe J., and Ueland, K Maternal cardiovascular adjustments to pregnancy Prog Cardiovasc Dis 46 363 1974
8 Burwell C S The placenta as a modified arteriovenous fistula considered in relation to the circulatory adju t ments to pregnancy Am J Med Sci 195 1 1938
9 Wartman, W Experimental arterial disease—The reac tion of the pulmonary artery to minute emboli of blood clot Circulation 4 747 1951
10 McKay D G Disseminated intravascular coagulation New York, 1965 Hoeber Medical Division Harper & Row p 396
11 Naeye R L Hagstrom J W C and Talmadye B A Postpartum death with maternal congenital heart disease Circulation 36 304 1967

Prophylactic anticoagulant therapy has been recommended for postpartum patients with Eisenmenger s syndrome by Neilson and others[2] on theoretical grounds These authors reasoned that, because of the high risk of pulmonary intravascular thrombosis with a consequent rise in pulmonary resistance anticoagulant therapy would be advisable immediately after delivery or after surgery ' We have followed this recom mendation in five of our patients with dismal outcome Although our study did not include, for comparison, a matched group of patients who did not receive anticoagulant therapy, our results with prophylactic heparin in therapeutic doses strongly suggest that the risk of bleeding outweighs the theoretical benefits from this drug Whether mini heparin doses will prove effica cious without the hazard of excessive bleeding in these patients remains to be proved In other puerperal patients we have seen no hemorrhages associated with mini doses of heparin However, it is noteworthy that several authors who initially recommended anticoagulant therapy in the man agement of pulmonary hypertension have later observed that such therapy did not prove effica cious and have subsequently recommended against its routine use[16]

The pathogenesis of death in Eisenmenger s syndrome remains an enigma and the mech anisms involved remain largely hypothetical Factors that decrease systemic resistance de crease blood volume or increase pulmonary resistance could adversely influence the outcome of this disease Bleeding not only leads to a decrease in blood elements necessary for adequate tissue oxygenation but also by virtue of the sudden drop of systemic pressure may tip the balance in favor of an increased right to left shunt which in turn leads to increased cyanosis and tissue hypoxia Furthermore the decrease in blood volume added to increased right to left shunting could lead to sufficient slowing of blood flow through the pulmonary circulation, and that may favor local arterial thrombosis This phenomenon could be further enhanced by the activated blood clotting mechanisms in response to bleeding [10] Stasis in previously diseased vessels plus induction of a hypercoaguable state by pregnancy and further by bleeding may result in thrombosis of preterminal pulmonary ar terioles In an already compromised pulmonary circulation, extensive thrombosis would not ne- to occur to cause irreversible hypoxia A vi- cycle of bleeding—thrombosis may explain t- the sudden and irreversible hemodynamic de- oration in patients M S and C S J (at the time of bleeding but 24 to 48 hours after t- blood loss had been corrected It appears th- progression of pathologic changes in the pul- nary vascular tree constitutes the major fa- underlying the prohibitive mortality rate o- Eisenmenger's syndrome during and immedia- after the termination of pregnancy Although t- clinical picture simulates closely that of acu- pulmonary artery occlusion autopsy studie- including our own have shown that the pulmonary arteries are usually free of clots therefore appears that increase in patholo- changes in the small pulmonary arteries underl- the progressive deterioration of these patients. has been postulated that rapid postpartum i- creases in pulmonary vascular resistance m- due to widespread thrombosis in previou- narrowed pulmonary arterial channels[11] S- preterminal thrombosis is more common patients with large shunts and elevated pul- nary arterial pressures who have been pregn- than in patients with comparable cardiac defe- who have never been pregnant [9] The pathog- esis of gestational thrombotic disorders is clear, but is manifested by certain blood coag- tion alterations which may be similar to disse- nated intravascular coagulation[11] If such indeed the case, heparin therapy could theor- cally have beneficial effects But the adv- effects of postpartum hemorrhage the possibi- of accentuation of intra alveolar bleeding c- bined with the increased propensity of pat- with Eisenmenger s syndrome to have coag- tion defects[14] seem to outweigh its possible be- fits In this series heparin induced hemorrh- appears to have played an important role in death of two of the five patients in whom it used

Hypoventilation bronchospasm, and bron- pulmonary disease not only would impair oxy- ation of blood in the pulmonary capillary bed also would increase the pulmonary vascular r- tance through vasoconstriction ' ' thereby creasing the right to left shunt and decrea- pulmonary blood flow The use of sedatives narcotics during labor and in the early puerp-

ng term angiographic assessment of the luence of coronary risk factors on native ronary circulation and saphenous vein rtocoronary grafts

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rtocoronary vein graft bypass surgery has ned widespread acceptance for the treatment angina pectoris Late graft patency rates have n variable but usually are reported between 75 d 85 per cent The study of factors affecting ft patency has primarily centered on surgical hnique characteristics of the vein graft and e of the distal vessel [6] Similarly the effects of pass grafting on the proximal and distal gments of the native grafted vessels have been udied [7-10] Acceleration of progression of obstruc ve disease in grafted vessels has been attributed changes in flow rates induced by the grafts and her mechanical factors [1]

Hyperlipidemia cigarette smoking hyperten on and diabetes mellitus are recognized risk ctors in the development of coronary artery isease [12] It is not surprising that a significant roportion of patients undergoing aortocoronary ypass surgery would be exposed to one or more f these risk factors Furthermore it is possible hat the presence of these risk factors could dversely affect graft patency and progression of bstructive disease in native vessels Allard and ssociates reported that hypertriglyceridemia ncreased their graft occlusion rate In this study we report the influence of hyperlipidemia smoking and diabetes on graft patency and progres sion of disease in native vessels in 99 patients assessed 1½ years after aortocoronary bypass surgery

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Patients and methods

From March 1969 to December 1972 at the Toronto General Hospital 314 patients had aortocoronary saphenous vein bypass grafts for stable angina The details of patient selection and operative techniques have been published else where [13] The in hospital mortality rate was 2 5 per cent The late cardiac mortality rate was 1 per cent over the entire follow up period Question naires were mailed to all patients with a request to return for follow up investigation One hundred patients volunteered to return for follow up 12 to 42 (mean 19 7) months postoper atively

In the follow up group graft patency and progression of disease in the native circulation were assessed in terms of three risk factors smoking glucose intolerance and serum lipid profiles Patients were considered nonsmokers if they had never smoked or had stopped before surgery Smokers consumed 20 cigarettes or more a day Glucose tolerance was assessed by blood sugar determinations of patients in the fasting state performed in the routine laboratory * A fasting level less than 120 mg per 100 ml (in plasma) was considered normal Serum lipid determinations* and electrophoresis† were per

*A to-A alyzer

†Zip Zone Electrophoresis with Titan III XW

12 Tuller M A Amniotic fluid embolism afibrinogenemia and disseminated fibrin thrombosis Am J Obstet Gynecol **73** 273 1957

13 Lung C J Am J Obstet Gynecol **55** 224 1940

14 Vessey M P and Doel R Investigation of relation between use of oral contraceptives and thrombo embolic disease Br Med J **2** 199 1968

15 Goodwin J F The Eisenmenger syndrome Prog Cardiol **3** 220 1974

16 Heath D and Edwards J E The pathology of hyper tensive pulmonary vascular disease Circulation **18** 533 1958

17 Grover R F and Weil J V Pulmonary hyperten[illegible] and pulmonary hypertensive heart diseases Cr[illegible] diagnosis 3 Philadelphia 1971 W B Saunders Co[illegible] ny p 291

18 Nakano J Prostaglandins and the circulation, M[illegible] Conc. Cardiovasc Dis **40** 49 1971

19 Buja L. M Freed T A Berman M A. Morrow A C. and Roberts, W C Pulmonary alveolar hemorr[illegible] Am J Cardiol **27** 168 1971

20 Naeye R L. and Vennart G P Structure and s[illegible] cance of pulmonary plexiform structures, Am. J Path[illegible] **36** 593 1960

ıg term angıographıc assessment of the ˈuence of coronary rısk factors on natıve ˈonary cırculatıon and saphenous veın tocoronary grafts

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ˈtocoronary veın graft bypass surgery has ıed wıdespread acceptance for the treatment ıngına pectorıs Late graft patency rates have n varıable but usually are reported between 75 l 85 per cent[1] The study of factors affectıng ft patency has prımarıly centered on surgıcal hnıque characterıstıcs of the veın graft and e of the dıstal vessel[2-4] Sımılarly the effects of pass graftıng on the proxımal and dıstal ɡments of the natıve grafted vessels have been ıdıed[5] Acceleratıon of progressıon of obstruc ve dısease ın grafted vessels has been attrıbuted changes ın flow rates ınduced by the grafts and her mechanıcal factors[6,7]

Hyperlıpıdemıa cıgarette smokıng hyperten on and dıabetes mellıtus are recognızed rısk ctors ın the development of coronary artery sease[8] It ıs not surprısıng that a sıgnıfıcant roportıon of patıents undergoıng aortocoronary ypass surgery would be exposed to one or more f these rısk factors Furthermore ıt ıs possıble hat the presence of these rısk factors could dversely affect graft patency and progressıon of bstructıve dısease ın natıve vessels Allard and ssocıates[9] reported that hypertrıglycerıdemıa ncreased theır graft occlusıon rate In thıs study we report the ınfluence of hyperlıpıdemıa smokıng and dıabetes on graft patency and progres sıon of dısease ın natıve vessels ın 99 patıents assessed 1½ years after aortocoronary bypass surgery

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In the follow up group graft patency and progressıon of dısease ın the natıve cırculatıon were assessed ın terms of three rısk factors smokıng glucose ıntolerance and serum lıpıd profıles Patıents were consıdered nonsmokers ıf they had never smoked or had stopped before surgery Smokers consumed 20 cıgarettes or more a day Glucose tolerance was assessed by blood sugar determınatıons of patıents ın the fastıng state performed ın the routıne laboratory A fastıng level less than 120 mg per 100 ml (ın plasma) was consıdered normal Serum lıpıd determınatıons* and electrophoresıs† were per

*Auto Analyzer
†Zip Zone Electrophoresıs wıth Tıtan III XW

Table I Influence of risk factors on graft patency

*No of risk factors**	*No of patients*	*Total grafts*	*No of patent grafts*	*Per cent patency*
None	24	34	27	79
1†	43	67	46	69
2‡	28	34	27	79
3	4	6	5	83
Totals	99	141	105	74

*Risk factors smoking hyperlipidemia and abnormal glucose tolerance

†There was no significant difference when factors were analyzed individually

‡Includes all combinations of two risk factors as there was no significant difference between combinations analyzed separately

$P > 0.1$ chi square test

Table II Influence of risk factors on progression

No of risk factors	*No of patients*	*Progression in grafted vessels†*				*Progression in nongrafted vessels†*	
		Proximal		*Distal*			
None	24	11	(20)	1	(31)	8	(48)
1	43	26	(49)	3	(58)	6	(87)
2	28	13	(20)	5	(26)	12	(52)
3	4	2	(3)	0	(5)	1	(7)
Totals	99	52	(92)	9	(120)	27	(194)

*As in Table I

†Numbers in parentheses = total assessed vessels at risk $P > 0.1$ chi square test

formed in the fasting state by the hospital laboratory A cholesterol level less than 250 mg per 100 ml and triglycerides less than 150 mg per 100 ml were considered normal Blood sugar and lipid levels were determined as part of both the preoperative and follow up assessment and the mean of the two determinations was used for this analysis One patient was excluded from analysis because lipid determinations were not performed during either assessment Statistical analysis was performed by the chi square test with P values noted in the tables

Cardiac catheterization was performed by standard techniques and included selective opacification of grafts and coronary arteries by Sones or Judkins' techniques Angiograms were recorded on 35 mm cine film with Phillips or Siemens image intensification equipment Extent of coronary disease was assessed independently by three experienced observers All three observers noted the same lesions When differences among the three observers in interpretation of severity of a lesion could not be resol[illegible] interpretation of the same senior cardio[illegible] radiographer was accepted throughout the st[illegible] The four major vessels were considered eq[illegible] lent and divided into grafted and nongra[illegible] vessels for analysis

Grafted vessels were considered to have [illegible] segments one proximal and one distal to th[illegible] graft anastomosis The left main coronary [illegible] considered a separate grafted vessel with a p[illegible] imal but no distal segment if both left ante[illegible] descending and circumflex arteries were graft[illegible] It was considered a nongrafted vessel if only [illegible] or neither branch was grafted Progression [illegible] considered to have occurred in a segment if t[illegible] degree of narrowing increased by one gr[illegible] (Grading I = less than 25 per cent, II = [illegible] to [illegible] per cent, III = 50 to 75 per cent IV = [illegible] to [illegible] per cent V = total occlusion) A vessel [illegible] considered to be at risk of progression onl[illegible] not totally occluded at the time of preopera[illegible] assessment

Results

This patient group consisted of 93 males a[illegible] seven females with a mean age of 52[illegible] ye[illegible] (range, 32 to 65), all having Class III to I[illegible] symptomatology preoperatively (New Y[illegible] Heart Association)[20] Only seven patients failed [illegible] improve by at least one class At postopera[illegible] assessment, 74 were in Class 0 to I Over all gr[illegible] patency rate was 74 per cent Clinical characte[illegible] istics and operative results of this patient gro[illegible] have been documented in detail[19] The progres[illegible] sion of disease in the native circulation and [illegible] relationship to graft patency and collaterals have been detailed previously[21, 22]

One patient did not have a serum lipid determi[illegible] nation either pre or postoperatively and was therefore excluded from analysis This patie[illegible] had two patent grafts had no progression in th[illegible] two proximal or two distal grafted segments [illegible] had shown progression in the one nongrafte[illegible] vessel at risk

There were 45 patients that were nonsmoker[illegible] Ninety patients had normal fasting blood suga[illegible] levels (mean 98 mg per 100 ml) and nine ha[illegible] abnormal blood sugar levels (mean 150 mg pe[illegible] 100 ml) There were 80 normocholesterolemi[illegible] patients (mean 201 mg per 100 ml) and 19 wit[illegible] hypercholesterolemia (mean, 280 mg per 100 ml[illegible]

y nine patients had normal triglycerides in 120 mg per 100 ml) and 50 elevated ycerides (mean 241 mg per 100 ml) Three ents were maintained on a lipid lowering drug fibrate) and two patients were on tolubuta e There was no significant difference between r preoperative and follow up lipid or blood ar status Thirty three of the 99 patients lost least one kilogram of weight from their operative to follow up assessment Two of se patients with weight loss had a sufficient rease in their preoperative elevated serum lesterol or triglyceride levels to be included in normal group after follow up assessment No ients with weight loss and abnormal preopera blood sugar reverted to the normal group

Twenty four patients were nonsmokers with rmal lipid and blood sugar levels When mpared with patients having one two or all ee risk factors there was no significant differ e in either graft patency (Table I) or rate of ogression of disease in the native circulation able II) Each risk factor was analyzed inde ndently as either an isolated risk factor or in mbination with either of the others As there is no significant difference found between the fferent risk factors singly or in combination for ese tables they have been grouped together and e patients classified on the basis of the number risk factors present

Of the 20 patients with hypercholesterolemia nd 50 with hypertriglyceridemia 11 had eleva ons of both The graft patency rate of these roups of patients is compared with patients with ormal lipids in Table III There was no signifi ant difference in graft patency rates in these roups Similarly these groups showed no signifi ant difference in rates of progression of disease Table IV) The influence of serum triglycerides n graft patency was further assessed by omparing the mean of preoperative and follow up triglyceride levels in patients with one or more grafts occluded to triglycerides in patients with all grafts patent The mean triglycerides in the 33 patients with at least one graft occluded was 166 mg per 100 ml (S D ± 72 mg per 100 ml) and 1?3 mg per 100 ml (S D ± 69 mg per 100 ml) in the 66 patients with all grafts patent This differ ence was not statistically significant ($p > 0.1$ Student s t test)

By lipoprotein electrophoresis 39 patients were normal 14 Type II and 46 Type IV These

Table III Influence of hyperlipidemia on graft patency*

Lipid abnormality	*No of patients*	*Total grafts*	*No of patent grafts*	*Per cent patency*
Normal lipids	41	61	45	74
Hypercholesterolemia only	8	9	8	89
Hypertriglyceridemia only	39	57	43	[illegible]
Hypercholesterolemia and hypertriglyceridemia	11	14	9	64
Totals	99	141	105	[illegible]4

$P > 0.1$ chi-square test

Table IV Influence of hyperlipidemia on progression

Lipid abnormality	*No of patients*	*Progression in grafted vessels*				*Progression in nongrafted vessels*	
		Proximal		*Distal*			
Normal lipids	41	21	(40)	2	(55)	11	(80)
Hypercholesterolemia only	8	3	(6)	1	(5)	1	(15)
Hypertriglyceridemia only	39	[illegible]	(37)	6	(49)	13	(74)
Hypercholesterolemia and hypertriglyceridemia	11	6	(9)	0	(11)	2	(19)
Totals	99	5[illegible]	(9[illegible])	9	(1[illegible]0)	27	(194)

Numbers in parentheses = total assessed vessels at risk $P > 0.1$ chi square test

groups corresponded with the divisions based on cholesterol and triglyceride levels except for patients with mildly elevated lipids in whom electrophoresis was normal. Graft patency rate was 74 per cent in normal subjects 73 per cent in Type II and 75 per cent in Type IV Rate of progression did not differ significantly between these groups and was similar to that shown in Table IV

Discussion

Hyperlipidemia smoking and diabetes mellitus are established risk factors in coronary artery disease [16] Little information is available on their

Table V Comparison of total and restudied groups at time of preoperative assessment

	Patients	Age mean ± S D	Males (%)	Smokers (%)	Blood pressure (mm Hg ± S D)		Blood su ar (fastin)	
					Systolic	Diastolic	No †	Mg /100 ml S
Total group	314	49 ± 7	89	52	134 ± 18	83 ± 11	314	96 ± 19
Restudied group	100	49 ± 8	93	60	135 ± 15	83 ± 10	100	9 16
Tests‡			C	C	T	T		T

	Cholesterol		Triglycerides		Lipid type			
	No †	Mg /100 ml ± S D	No †	Mg /100 ml ± S D	Normal	Type 2	Type 4	Total
Total group	312	222 ± 47	286	173 ± 97	112(41)§	33(12)	128(4)	9 3
Restudied group	99	225 ± 49	99	166 ± 67	39(39)	14(14)	46(46)	99
Tests		T		T	C	C	C	

	Disease extent			Total grafts	Grafts per patient
	1 vessel	2 vessel	3 vessel		
Total group	44(14)§	105(33)	165(53)	438	1 4
Restudied group	14(14)	30(30)	56(56)	143	1 4
Tests	C	C	C	C	C

Smokers—20 or more cigarettes per day at time of preoperative catheterization
†Number—number of patients with appropriate data determined at time of preoperative catheterization
‡C chi square T Student s t test P > 0 5
§Number of patients followed by percentage in parentheses

influence on graft patency and progression of obstructive disease in native vessels after aorto coronary bypass surgery

Glassman and his co workers[24] recently found that diabetes mellitus had no influence on progression of disease or graft patency following aortocoronary bypass surgery over a follow up period of 9 4 months The influence of hyperlipi demia and smoking on progression as well as patency has not yet been examined

In this study, 99 patients volunteered to return for follow up selective coronary and graft arteri ography over 1½ years (mean) after aortocor onary bypass surgery Any such study predicated on voluntary follow up introduces the possibility of an uncontrolled bias Previous reports have suggested this bias is toward the return of symp tomatically worse patients[25, 26] However Griffith and associates[10] could not demonstrate any bias in their study of a voluntary follow up group

We compared our follow up group with the total cohort with respect to the risk factors studied, extent of disease and number of grafts (Table V) We also compared age, sex, and blood pressure There was no significant differer between the restudied group and the parent gro in respect to any of these variables (p > 0 5)

A significant proportion of these 99 patie were hyperlipidemic (59 patients) smokers (4 patients), and diabetic (9 patients) allowing meaningful numbers in most groups of patients Previous reports from ourselves and other centers have established graft patency rates and rates of progression of disease in proximal and distal segments of grafted native vessels and nongrafted vessels[7, 10, 19, 21, 22] In our *control* group of 9 patients with no risk factors the graft patency rate was 79 per cent Over the follow up period the rate of progression of obstructive disease in proximal segments of grafted vessels was 55 per cent and the rate of progression in distal grafted vessels was 3 per cent in the control group In nongrafted vessels the progression rate was 1 per cent These graft patency and progression rates are comparable to previous reports and can be taken as acceptable control values

Patients were divided into groups according to the presence of one only, two, and three ri k

rs As outlined in Table I there was no ·ence in graft patency rates between the ol group and groups with one two, or three ·actors When smoking hyperlipidemia and rmal glucose tolerance in patients with a e risk factor were analyzed independently was again no significant difference in graft ncy Similarly when combinations of two factors—for example smoking plus hyperlipi ia—were analyzed independently in the group atients with two risk factors no significant rence in graft patency was present The ip with all three risk factors was small but etheless their graft patency rate was almost itical to that of the control group Patients n hyperlipidemia were further subdivided into se with hypercholesterolemia alone hypertri ·eridemia alone or both together There was significant difference in graft patency rates ween any of these groups and the control up

'revious reports from Allard and associates[1 8] icated that hypertriglyceridemia is associated h an increased rate of graft occlusion They icluded that hypertriglyceridemia was a risk tor for graft occlusion and that this effect ild be related to impaired fibrinolytic activity luced by hypertriglyceridemia This association hypertriglyceridemia with increased graft clusion was not apparent in our study We have mpared graft patency rates in groups with rmal vs elevated mean triglyceride levels and ve also used Allard s method of comparing glyceride levels in groups with occluded vs tent grafts No association of increased triglyc ides with graft occlusion could be demonstrated either method Specifically the mean trigly ride level in patients with one or more occluded afts (166 mg per 100 ml) was not significantly fferent from the level in patients with patent afts (173 mg per 100 ml) as opposed to the sults of Allard and associates The results of our udy suggest that hypertriglyceridemia is not a isk factor for graft occlusion over this period of ime

Hyperlipidemia smoking and abnormal glucose olerance are generally accepted as risk factors for icceleration of atherosclerotic disease in the oronary arteries A significant proportion of our patients had one or two of these risk factors and therefore might reasonably be expected to have increased progression of obstructive disease after bypass surgery Table II compares the progres sion of obstructive disease in grafted and nongrafted vessels in patients with no risk factors one two and three risk factors As discussed in previous publications the rate of progression of disease is high in proximal segments of grafted vessels[7 10] This high rate is most probably second ary to mechanical factors such as changes in flow induced by grafting[10 11] It is perhaps not surprising then that the presence of one two or three risk factors had no discernible effect on the proximal progression rate Similarly as outlined in Table IV the presence of hypercholesterol emia hypertriglyceridemia or both together was not associated with an accelerated effect on prox imal progression compared to the control group

The rates of progression of disease in distal segments of grafted vessels have been reported from low to moderately high[7 1] In our series the over all distal progression rate was 7 per cent Table II illustrates that the presence of one two or three risk factors had no significant effect on distal progression The distal progression rate with two risk factors (five of 26) is higher than the control group (one of 31) but this difference was not statistically significant As outlined in Table IV hypercholesterolemia alone had no adverse effect on distal progression Distal progression with hypertriglyceridemia alone (six of 49) was slightly higher than in the control group but again not with statistical significance The number of vessels with distal progression is low however and this could possibly obscure a signif icant influence of hypertriglyceridemia or other risk factors

The problem of small numbers of vessels subjected to risk factors is in part satisfied by the study of nongrafted vessels The group of nongrafted vessels at risk of progression is a large group which has not been subjected to surgical manipulation or changes in flow patterns induced by competitive graft flow An adverse influence of risk factors should be most apparent in this group of vessels Tables II and IV however indicate that no single or combination of risk factors had any significant effect on acceleration of progres sion over this follow up period In particular the progression rate in vessels subjected to two risk factors or hypertriglyceridemia alone was not significantly different from the rate in the control

Table V Comparison of total and restudied groups at time of preoperative assessment

	Patients	*Age mean ± SD*	*Males (%)*	*Smokers (%)*	*Blood pressure (mm Hg ± SD)* *Systolic*	*Diastolic*	*Blood sugar (fasting)* *No†*	*Mg/100 ml ± SD*
Total group	314	49 ± 7	89	52	134 ± 18	83 ± 11	314	96 19
Restudied group	100	49 ± 8	93	60	135 ± 15	83 ± 10	100	9 15
Tests‡			C	C	T	T		T

	Cholesterol		*Triglycerides*		*Lipid type*			
	No†	*Mg/100 ml ± SD*	*No†*	*Mg/100 ml ± SD*	*Normal*	*Type 2*	*Type 4*	*Total*
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Tests		T		T	C	C	C	

	Disease extent			*Total grafts*	*Grafts per patient*
	1 vessel	*2 vessel*	*3 vessel*		
Total group	44(14)§	105(33)	165(53)	438	14
Restudied group	14(14)	30(30)	56(56)	143	14
Tests	C	C	C	C	C

Smokers—20 or more cigarettes per day at time of preoperative catheterization
†Number—number of patients with appropriate data determined at time of preoperative catheterization
‡C chi square T Student's t test P > 05
§Number of patients followed by percentage in parentheses

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group Therefore, we conclude that these coronary risk factors had no adverse influence on progression of obstructive disease for this length of follow up period

This study also points out the problem of patient compliance Forty five per cent of patients continued to smoke after surgery despite their physician's advice to stop The motivation to stop smoking should be considerably increased by the prospect of cardiac surgery and yet nearly one half of the patients did not respond The problem of poor patient compliance may make control of other risk factors as difficult and reduce potential benefits of bypass surgery This problem may require more attention as long term survivors of bypass operations are followed

In conclusion, the presence of hyperlipidemia, smoking, and abnormal glucose tolerance had no discernible adverse effect on graft patency or progression of obstructive disease in grafted and nongrafted vessels The development of coronary artery disease spans several decades in man Even in the presence of risk factors several years may be required before a significant difference in obstructive disease can be detected by coronary arteriography Longer follow up periods will therefore be required to clarify effects of these risk factors on aortocoronary bypass grafts and native vessels

Summary

The influence of smoking hyperlipidemia and glucose intolerance on graft patency and rate of progression of obstructive disease in the native circulation was assessed in 99 patients 1½ years after aortocoronary bypass grafting There were 24 patients in whom none of these risk factors was identified There were 42 patients with one 29 with two and four with three risk factors Overall graft patency rate was 74 per cent Graft patency was not significantly influenced by any of these factors either singly or in combination Progression of obstructive disease in both proximal and distal segments of grafted vessels and in nongrafted vessels was not significantly increased by the presence of one, two, or three risk factors Over all there was progression in 56 per cent of segments proximal to grafts, in 8 per cent distal to grafts and in 14 per cent of nongrafted vessels Longer term studies will be required to establish any adverse influence of these risk factors on saphenous vein bypass grafts and native circulation

REFERENCES

1 Dunkman W B Perloff J K Kastor J A Shelburne J C Medical perspectives in coronary artery surgery—a caveat Ann Intern Med 81 817 1974
2 Johnson W D Surgical techniques of myocardial revascularization An overview Bull N Y Acad Med 48 1146 1972
3 Jones M Conkle D M Ferrans V J Roberts W C Levine F H Melvin D B and Stinson E B Lesions observed in arterial autogenous vein grafts Light and electron microscopic evaluation Circulation 47-48 (Suppl III) III-198 210 1973
4 Bourassa M G Lespérance J Campeau L and Simard P Factors influencing patency of aortocoronary vein grafts Circulation 45-46 (Suppl I) I 79-85 1972
5 Walker J A Friedberg H D, Flemma R J and Johnson W D Determinants of angiographic patency of aortocoronary vein grafts Circulation 45-46 (Suppl I) I-86 90 1972
6 Lespérance J Bourassa M G Biron P Campeau L and Saltiel J Aorta to coronary artery saphenous vein grafts Preoperative angiographic criteria for successful surgery Am J Cardiol 30 459 1972
7 Maurer B J Oberman A Holt J H Jr Kouchoukos N T Jones W B Russell R O Jr and Reeves T J Changes in grafted and non grafted coronary arteries following saphenous vein bypass grafting Circulation 50 293 1974
8 Glassman E Spencer F C Krauss K R Weisinger B and Isom O W Changes in the underlying coronary circulation secondary to bypass grafting Circulation 50 (Suppl II) II-80 83 1974
9 Malinow M R Kremkau E L Kloster F E Bonchek L I and Rosch J Occlusion of coronary arteries after vein bypass Circulation 47 1211 1973
10 Griffith L S C Achuff S C Conti C R Humphries J O Brawley R K Gott V L and Ross R S Changes in intrinsic coronary circulation and segmental ventricular motion after saphenous vein coronary bypass graft surgery N Engl J Med 288 589 1973
11 Kakos G S Oldham H N Jr Dixon S H Jr Davis R W Hagen P O and Sabiston D C Jr Coronary artery hemodynamics after aorto-coronary vein bypass An experimental evaluation J Thorac Cardiovasc Surg 63 849 1972
12 Gordon T and Kannel W B Predisposition to atherosclerosis in the head heart and legs The Framingham Study J A M A 221 661 1972
13 Goldstein J L Hazzard W R Schrott H G Bierman E L and Motulsky A G Hyperlipidemia in coronary heart disease I Lipid levels in 500 survivors of myocardial infarction J Clin Invest 52 1533 1973
14 Salel A F Riggs K Mason D T Amsterdam E A and Zelis R The importance of type IV hyperlipoproteinemia as a predisposing factor in coronary artery disease Am J Med 57 897 1974
15 Dick T B S and Stone M C Prevalence of three cardinal risk factors in a random sample of men and in patients with ischemic heart disease Br Heart J 35 381 1973
16 Falsetti H L Schnatz J D Greene D G and Bunnell I L Lipid and carbohydrate studies in coronary artery disease Circulation 37 184 1968

Allard C Ruscito O and Goulet C The influence of serum triglycerides on the fate of aorto-coronary vein grafts, Can Med Assoc J 107 213 1972

Allard, C Goulet C Grondin C M Lespérance J and Bourassa M G Patency of aortocoronary vein grafts and serum triglycerides Three year follow up study Am J Cardiol 33 6 9 1974

Morch, J Morton B McLaughlin P Betriu A Aldridge H Schwartz L., Adelman A Wigl D McLoughlin M Goldman B Key J Bigelow W and Trimble A Late results of aorto coronary bypass grafts in 100 patients with stable angina pectoris Can Med Assoc J 111 5?9 1974

New York Heart Association Diseases of the heart and blood vessels Nomenclature and criteria for diagnosis, ed 6 Boston 1964 Little Brown & Company p 11?

McLoughlin M McLaughlin P Morton B Trimble A and Morch J Long term evaluation of progression of disease and fate of collaterals in aorto coronary bypass surgery Circulation 49 50 (Suppl. III) III-67 1974 (abst)

22 McLaughlin P R Berman N D Morton B C., McLoughlin M Aldridge H F Adelman A G Goldman B S Trimble A S and Morch J E Saphenous vein bypass grafting Changes in native circulation and collaterals Circulation 52 1-66 1975

23 Fredrickson D S and Lees R S A system of phenotyping hyperlipoproteinemia Circulation 31 321 1965

24 Engelman R M Bhat J G., Glassman E., Spencer F C Boyd A. D Pasternak, B S Reed G F and Isom O W The influence of diabetes and hypertension on the results of coronary revascularization Am J Cardiol 35 135 1975 (abst)

25 Anderson R. P Rahimtoola S H Bonchek L. I., and Starr A The prognosis of patients with coronary artery disease after coronary bypass operations, Circulation 50 274 1974

26 Alderman E L., Matlof H J., Wexler L., Shumway N E and Harrison D C Results of direct coronary artery surgery for the treatment of angina pectoris N Engl J Med 288 535 1973

Experimental analysis of development of cardiac insufficiency in old age

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Development of cardiac insufficiency in old age is a final result of the development of most diverse pathological processes and it is therefore a very frequent cause which limits the human lifespan That is why it is so important for the modern cardiologist to know the *metabolic*, structural, and functional mechanisms which determine the peculiarities of onset and the course of cardiac insufficiency in old age At the same time in the colossal literature dealing with the problem of cardiac insufficiency little attention is given to experimental analysis of age related peculiarities of its development While modeling the increased load upon heart by aorta coarctation we got some data on the mechanism of the development of cardiac insufficiency in old age They are given in the present article

Material and methods

Experiments were made on animals of two age groups They were rabbits (adult 12 to 14 months old, and 48 to 54 months old) and rats (aged 8 to 10 months and 26 to 28 months respectively) Aorta coarctation was made by modification[2] of Beznak's method[1] Rings to be placed around the aorta were selected to decrease aorta lumen 2 to 2 5 times and differences in the aorta lumen of adult and old rats were taken into account Hemodynamic indices were determined by the thermodilution method[3, 4] Intraventricular pressure was registered with an Electromanometer Model EM2 01 (Hungary) The maximal rat[illegible] increase of intraventricular pressure (dP/dt m[illegible] was recorded with a differential circuit Con[illegible] tility index was calculated by the method [illegible] Veragut and Krayenbuhl[5] Cardiac insuffic[illegible] phasic structure was determined by the meth[illegible] of Blumberger,[6] and adenylic nucleotides by th[illegible] method of low voltage paper electrophore[illegible] Inorganic phosphorus was obtained by modi[illegible] tion of the method of Fiske and Subbar[illegible] Lowry and Lopez[9] and of Skulachev [illegible] Glic[illegible] was determined by modification of Pflu[illegible] method[11] and pyridine coenzymes by the meth[illegible] of Kuft and Perlgweig[1] Pyruvate data w[illegible] obtained by the paper chromatography method and lactate in tissues by the method of Dische[illegible] Protein was obtained by the biuretic method Morphologically the heart was studied in h[illegible] topographic sections For electronmicroscopic study the pieces of beating heart were fixed in [illegible] per cent solution of glutaraldehyde and 1 per ce[illegible] osmic acid, when imbedded in Epon 812 Sectio[illegible] were made on ultratome 1KB and studied u[illegible] JEM 100B electron microscope The number a[illegible] size of mitochondria were measured using th[illegible] techniques described by Weibel and associates

Results

Experiments performed on rabbits and rats of different ages revealed significant changes i[illegible] hemodynamics and contractile capacity of the myocardium Table I shows that in old rabbit[illegible] there is a decrease in blood minute and stroke volumes *working index of the left ventricle* dP dt max contractility index a *shortening* of systole and some elongation of *diastole* [illegible], increase in the total peripheral resista[illegible] vessels In old rats (Table II) we ob[illegible]

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Table I Indices of myocardial hemodynamics and contractile capacity in rabbits of different ages

Indices	Adult M ± m †	Old M ± m	P‡
Systemic arterial pressure (mm Hg)	93 8 ± 2.2	96 5 ± 1 6	> 0 1
Heart rate (beats/min)	2 0 7 ± 6 2	258 2 ± 6.0	> 0 2
Cardiac output (mL/min)	304 0 ± 7 0	254 0 ± 11 0	< 0 0?
Stroke volume (mL)	1.2 ± 0 06	0 85 ± 0 04	< 0 0?
Systemic vascular resistance (dyn sec cm)	2 663 ± 851	31519 ± 149?	< 0 02
Cardiac index (L/min /M)	2 00 ± 0 08	0 99 ± 0 05	< 0 01
Left ventricular minute work index (kg./M)	2.50 ± 0 08	1 28 ± 0 07	< 0 01
Left ventricular pressure (mm Hg)	113 4 ± 4 2	103 5 ± 3 7	> 0 05
Maximal rate of rise of left ventricular pressure (mm Hg/sec)	33 5 ± 273	2480 ± 196	< 0 05
Contractility index (Relative Units)	?3 7 ± 5 0	61 2 ± 2.8	< 0 05
Intensity of structural functioning (mm Hg/G)	22 0 ± 2 0	16 4 ± 1 0	< 0 05
Duration (in sec) of			
Tension period	0 038 ± 0 001	0 051 ± 0 001	< 0 001
Asynchronous contraction	0 0?7 ± 0 001	0 033 ± 0 001	< 0 005
Isometric contraction	0 011 ± 0 001	0 018 ± 0 001	< 0 002
Ejection period	0 089 ± 0 002	0 098 ± 0 001	< 0 01
General systole	0 127 ± 0 002	0 149 ± 0 002	< 0 02
Mechanical systole	0 096 ± 0 001	0 108 ± 0 001	< 0 05
Diastole	0 091 ± 0 001	0 086 ± 0 002	> 0 05
Heart weight (G)	8.7 ± 1 1	11 3 ± 2.0	> 0 5
Width of left ventricular wall (mm)	6 3 ± 0 5	8 1 ± 0 3	< 0 01

M = mean valu
†m = st ndard error
‡P = les l f significan e

decrease in minute and stroke volumes working index of the left ventricle cardiac index dP/dt max and cardiac rhythm

Age related changes in heart contractile capacity are getting more pronounced under conditions of increased load upon myocardium after aorta coarctation As is known aorta coarctation results in the development of myocardial hyperfunction which has a phase development In case the load is excessive to structural and functional capacities of the myocardium a cardiac insufficiency develops We have correlated the shifts in hemodynamics and contractile capacity of the myocardium of adult animals which appeared on the fourth to seventh and on the fourteenth to sixteenth day after aorta coarctation i e according to Meerson[17] at an emergency stage (acute stage) and at a stage of relatively stable myocardial hyperfunction

As is seen in Table II insignificant changes in hemodynamics and contractile capacity of myocardium appear in adult rats on the fourth to seventh day after aorta coarctation whereas in old animals objective signs of cardiac insufficiency develop i e significant decrease in blood minute and stroke volumes cardiac index dP/dt max and contractility index Furthermore 40 per cent of old animals (8 out of 20) died within two or three days from acute cardiac insufficiency characterized by abrupt decreased of myocardial contractile capacity pulmonary edema hemorrhages into the myocardium exudate into thoracic and abdominal cavities and blood congestion in liver In the group of adult animals only two out of 17 (11 1 per cent) died within the same time period Age related changes are insignificant On the fourteenth to sixteenth day following aorta coarctation (Table II) the indices of myocardial hemodynamics and contractile capacity of adult animals increased substantially whereas in a number of old animals they are only returning to initial levels Changes of cardiac activity at aorta coarctation are pronounced in all old animals differently In one group of them there develop significant manifestations of cardiac insufficiency i e a fall in minute volume up to 30 ml /min a fall in dP/dt max to 650 mm Hg/sec and a fall in contractility index to 3 relative units At the same time the shifts in the hemodynamic indices of some old animals do not differ much from those of adult rats

To characterize potential capacities of myocar

ncar

Table II Changes in *myocardial hemodynamics and contractile capacity on the 4 7th day* (emerg stage) and the 14 16th day (*stage of relatively stable myocardial hyperfunction and hypertrophy*) after aorta coarctation in animals of different ages

Indices	*Old*		
	Control	*4 7th day*	
	$M \pm m$ †	$M \pm m$	P‡
Cardiac output (ml /min)	92 6 ± 3 0	74 3 ± 9 1	>0 05
Stroke volume (ml)	0.22 ± 0 02	0 21 ± 0 01	>0 5
Systemic arterial pressure (mm Hg)	79 0 ± 8 2	83 7 ± 6 8	>0 05
Heart rate (beats/min)	349 ± 21	349 ± 26	>0 5
Cardiac index (L /min /M²)	1 890 ± 0 02	1 665 ± 0 04	<0 05
Left ventricular minute work index (Kg /M)	2 016 ± 0 18	2 175 ± 0 21	<0 05
Systemic vascular resistance (dyn sec cm)	68329 ± 8241	94962 ± 9124	<0 05
Left ventricular pressure (mm Hg)	89 7 ± 3 1	103 2 ± 5 6	<0 05
Maximal rate of rise of left ventricular pressure (mm Hg/sec)	3378 ± 250	4700 ± 720	<0 05
Contractility index (Relative Units)	60 0 ± 2 3	69 4 ± 2 8	<0 05
Intensity of structural functioning (mm Hg/G)	14 2 ± 1 0	12 8 ± 0 8	>0 05

M = mean value
†m = standard error
‡P –P = level of significance (versus control value)

dium at different stages of development of its hyperfunction we used a test with complete aorta clamping [18] Fig 1 shows that a complete three time 30 second clamping of rat aorta on the fourth to seventh day following aorta coarctation results in a fall of intraventricular pressure dP/dt max contractility index, and finally in the death from heart failure in 63 per cent of old animals In adult animals the same conditions cause a sharp increase in the indices of myocar dial contractile capacity On the fourteenth to sixteenth day complete aorta clamping causes a pronounced increase in adult animals and an insignificant increase in old animals of myocar dial contractile capacity Thus the test with maximal load testifies to a sharp reduction of potential possibilities of myocardial contractile capacity in old animals

With age some changes occur in the neurohu moral regulation of the cardiovascular system This fact is supported by the changes in norepi nephrine content in various parts of the heart and particularly by changes in heart activity in response to stimulation of *norepinephrine sim paticus* In aging, the content of norepinephrine in the myocardium is decreased As is seen in Table III, this decrease is pronounced in a different manner in different parts of the heart Thus the norepinephrine content in the atria is decreased by 39 per cent as compared with adult animals in the right atrium by 37 per cent and in the left atrium by 18 per cent In old animals the stimulation of the sympathetic nervous system produces a less pronounced increase in blood minute volume With age the sympathetic effects upon the heart are weakened Upon stimulation of stellate ganglion by a 2 volt electric current the increase of minute volume in adult rats was 11 ± 1 4 ml /min as compared with 1 0 ± 4 0 ml /min in old rats at a 4 volt current the increase was 24 0 ± 10 2 and 7 6 ± 3 5 ml /min respectively The maximal increase (14 3 ± 4 2 ml /min) of minute volume in old animals was registered during stimulation by a 10 volt cur rent

At an emergency stage of the process the norepinephrine content (Table III) in different parts of heart of old animals tends to increase (atria right and left ventricle) By the fourteenth to sixteenth day the norepinephrine content in the atria and right ventricle is increased while in the left ventricle it is decreased At an emergency stage the norepinephrine content in the atria and right ventricle is becoming increased while in the left ventricle it remains unchanged At a stage of relatively stable hyperfunction the norepineph rine content in either part of the heart is decreased

The above age related changes in myocardial function have a definite metabolic background

		Adult				
14-16th day		*Control*	*4 7th day*		*14 16th day*	
$M \pm m$	P	$M \pm m$	$M \pm m$	P	$M \pm m$	P
10 0 ± 4.8	< 0 05	76.? ± 2.4	40 0 ± 3 ?	< 0 001	72 0 ± 2.8	> 0.5
0 27 ± 0 0?	< 0 05	0 ?1 ± 0 01	0 1? ± 0 04	< 0 01	0 18 ± 0 01	> 0 05
790 ± 4 9	> 0 5	84 2 ± 2 6	780 ± 3 8	> 0 05	85 0 ± 2 7	> 0 05
39 ± ?1	> 0 05	335 ± 10	327 ± 24	> 0 05	377 ± 15	> 0 05
2 03 ± 0 06	< 0 01	1 342 ± 0 06	0 796 ± 0 04	< 0 0?	1 423 ± 0 04	< 0 05
2541 ± 0 08	< 0 05	1 ?99 ± 0 03	0 732 ± 0 04	< 0 05	1 637 ± 0 1	< 0 05
62215 ± 4614	> 0 05	14898? ± 134?1	88310 ± 2?81	< 0 05	99031 ± 5464	> 0 05
9 5 ± 2.7	> 0 05	92.0 ± 3 0	90 9 ± 4 7	> 0 05	97.3 ± 2.4	> 0 05
5410 ± 818	< 0 01	2650 ± 189	?050 ± 111	< 0 05	3080 ± 449	> 0 05
83 0 ± 4 7	< 0 01	47 4 ± 3 9	?(2 ± 4 0	< 0 01	42 8 ± 2.6	> 0 05
10 0 ± 1 2	< 0 05	8 3 ± 0 4	9 9 ± 0 6	< 0 05	9 4 ± 0 7	> 0 05

(Table IV) With age the concentration of adenosine triphosphoric acid (ATP) and especially that of creatine phosphate (CP) is decreased At the same time the increase of concentration of adenosine monophosphate (AMP) and IP results in a reduction of the energetic change of myocardial cells which according to Atkinson[9] is 1(ADP) + 2(ATP)/2(AMP) + (ADP) + (ATP) In adult rats it equals to 0 61 and in old rats it is 0 5 The above shift in energetic charge obviously accelerates the processes accompanied by accumulation of ATP and *inhibits the reactions* which utilize it The increase in phosphorylation coefficient (ADP) (IP)/(ATP) from 4 2 ± 0 2 to 5 2 ± 0 2 (p > 0 05) *also serves* in favor of the strengthening of energetic metabolism intensity There is a decrease in glycogen and pyruvate content and an increase in lactate concentration in an old heart which results in a decrease of pyruvate/lactate ratio Alongside the increased content of lactate restored NAD decreased NAD/NAD H_2 coefficient this testifies to the intensification of anerobic transformations in the heart s energetic metabolism to changes in the respiration/glycolysis ratio in favor of the latter Thus under normal conditions essential changes take place in the course of energetic processes of an old heart which may limit its potential functional possibilities and promote the development of occult cardiac insufficiency in old age This can be clearly seen under conditions of load (in our experiments with aorta coarctation) (Table V) Thus on the fourth to seventh day after operation the concentration of adenine nucleotides in adult hearts does not change significantly whereas in old animals there is an *increase in* ADP content and a decrease in AMP concentration and what is especially important a twofold decrease of CP *concentration* At the same time the lactate concentration is significantly increased in an old heart testifying to the development of hypoxia disturbances in lactate transformation and limitations in the utilization of glycolysis products in biosynthetic reactions

Age peculiarities of changes of different indices of energetic metabolism in the myocardium still remain on the fourteenth to sixteenth day following aorta coarctation In an adult heart the concentrations of ATP CP and glycogen are increased significantly (p < 0 05) *whereas in the* myocardium of old animals the concentration of ATP remains unchanged that of CP is getting restored (but not *reaching the initial level*) while the glycogen concentration continues to decline thus weakening the heart stability to the *worsening of conditions of its activity* and affecting the functional state of the myocardium Age peculiarities can also be observed while counting the data obtained per the weight of the whole heart (Fig 2 initial values are taken as 100 per cent) The

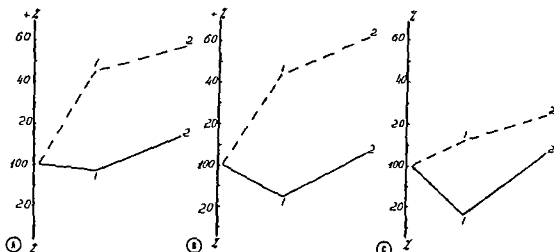


Fig 1 Contractile capacity of left ventricle in rats of different ages on the fourth to seventh days and on the fourteenth to sixteenth days following aorta coarctation *A* maximal systolic pressure *B* maximal rate of tension development in myocardium *C* Contractility index *1* fourth to seventh day following aorta coarctation *2* fourteenth to sixteenth day following aorta coarctation *Broken line* = adult rats *solid line* = old rats

analysis of these correlations reveals the age peculiarities of heart reactions to aorta coarctation at various periods of their development Alongside hypertrophy of the myocardium the content of energetic substrates and metabolites is increased in adult animals, resulting in their retaining their concentrations per unit of myocardial mass

While evaluating the data obtained, consideration should be given to the fact, that, as has already been mentioned, the overwhelming majority of old animals died within the first few days after aorta coarctation from progressive cardiac insufficiency By the fourteenth to sixteenth day only part of them survived Probably these animals were more viable having less pronounced changes in heart metabolism Still, as Fig 2 shows the changes in content of separate components of adenylic system, glycogen, and lactate are less optimal in old animals than in adults

As is known, aorta coarctation induces heart hyperfunction, resulting in activation of the genetic apparatus and an intensification of protein biosynthesis, which lead to hypertrophy of the myocardium The dynamics of the heart s weight may serve as an indication for the development of its hypertrophy On the fourth to seventh day following aorta coarctation there was a pronounced increase of weight of different parts of heart (atria–from 61 6 ± 3 21 to 105 3 ± 9 8 mg, right ventricle–from 151 5 ± 4 8 to 178 5 ± 5 6 mg, left ventricle–from 527 2 ± 12 1 to 734 2 ± 18 2 mg) By the fourteenth to sixteenth day there was a corresponding weight increase in the atria–to 106 3 ± 10 4 mg, right ventricle–194 5 ± 14 1 mg left ventricle–790 3 ± 31 8 mg It should be noted that the increase was observed both in absolute and in relative heart weight An old rat heart weighs on an average 251 3 mg more than an adult heart At the same time the total heart weight, both absolute and the relative, does not change significantly within the above period Of all the heart parts of old rats significant weight increase (from 87 0 ± 4 4 to 100 6 ± 3 4 mg) was observed in atria only Thus aorta coarctation and increased load do not lead to the development of myocardial hypertrophy in old animals Changes in heart weight and morphological data serve as evidence for this Thus, in adult animals there was a sharp reduction of nuclear-cytoplasmic index (prior to aorta coarctation 0 35, on the fourth to sixth day after coarctation, –0 24, on the fourteenth to sixteenth day 0 21) at the expense of the increase of cytoplasm the volume of which is almost doubled in cells of subendocardial parts In old animals the reduction of nuclear-cytoplasmic index and the increase of cytoplasm are statistically insignificant (prior to coarctation 0 21 fourth to sixth day after coarctation, 0 18, fourteenth to sixteenth day after coarctation, 0 21) The heart of old rats is somewhat hypertrophied already under normal conditions Within the studied periods following aorta coarctation there was no significant increase in weight and diameter of myocardial fibers

Changes in content of separate protein frac

Table III Changes in norepinephrine content in heart of animals of different ages at hyperfunction and hypertrophy of myocardium (μg/G wet weight)

Age (mos)	Statistical indices	*Atria*			*Right ventricle*			*Left ventricle*		
		Control	*5 7th day*	*14 16th day*	*Control*	*4 7th day*	*14 16th day*	*Control*	*4 7th day*	*14 16th day*
8-10	M	2 59	3 1	1.24	1.31	2.2	0 92	0.9	0 9	0 43
	m†	0 ?06	0 244	0 07	0 14	0.2	0 12	0 05	0 07	0 04
	Px‡		>0 05	<0 001		<0 001	<0 0?			<0 001
24 ?6	M	1 59	2.5	2.23	0 83	1.99	0.93	0 74	0.97	0 63
	m	0 17	0 24	0 36	0 123	0 111	0 08	0 052	0 07	0 14
	Px		<0 001	>0 05		<0 001	>0 0?		<0 01	>0 2

M = m an alues
†m = standard error
‡Px = as comp red with ntrol

tions following aorta coarctation serve as another evidence for the limitation of biosynthetic processes in the heart of old animals The concentration of total protein and water soluble proteins mainly sarcoplasmic proteins (myo albumin myoglobin myogen) is decreased in the heart of old animals (Table VI) At the same time the concentration of water insoluble nonsclero proteid myofibrillar contractile proteins (myosin actin actomyosin etc) is increased The concentration of collagen is also increased This obviously determines the age peculiarities of changes in protein content following aorta coarc tation (Table VI) On the fourth to seventh day after operation there is an insignificant decrease in concentration of water insoluble myofibrillar proteins and a significant increase in concentra tion of total protein in animals of both age groups In the heart of adult rats there is also a significant increase in the concentration of labile collagen On the fourteenth to sixteenth day however the concentration of water insoluble contractile proteins continues to decrease and the content of water soluble mainly sarcoplasmic proteins is decreased significantly whereas in adult rats the concentration of protein fractions in the myocardium is returning to the initial level Age peculiarities are also revealed while counting the data obtained per the whole heart weight (Fig 3 initial values are taken as 100 per cent) The above shifts testify to the weakening of capacity of an old myocardium to regular inten sive biosynthesis of all protein fractions under the conditions which require the development of compensatory hypertrophy and the increase of myocardial contractile capacity

Table IV Indices of energetic metabolism of the myocardium of rats of different ages

	Age (months)	
	8-12	*28-32*
ATP (μmoles/G)	1 41 ± 0 03	1 10 ± 0 05
ADP (μmoles/G)	0 89 ± 0 02	0 65 ± 0 04
AMP (μmoles/G)	0 71 ± 0 02	0 92 ± 0 05
CP (mg %)	7 54 ± 0 13	3 ?0 ± 0 27
IP (mg %)	21 10 ± 1 ?0	27 60 ± 2.01
Glycogen (mg %)	596 90 ± 20 50	338 40 ± 27.90
Pyruvate (μmoles/G)	0 18 ± 0 02	0 13 ± 0 01
Lactate (μmoles/G)	0 78 ± 0 02	1 17 ± 0 02
Pyruvate/lactate (1 10)	23.5	11 1
NAD + NADP (μg/G)	290 30 ± 12 40	295 90 ± 8 90
NAD H + NADP H (μg/G)	164.90 ± 14 90	215 20 ± 13 90
NAD+NADP/NAD H +NADP H	2.02 ± 0 21	1 43 ± 0 07

Statistically significant differences ($p < 0.05$)

We have identified distinct age related differ ences in the course of separate phases of heart hyperfunction Thus the correlation of the data obtained shows that at the stage of stable hyper function of adult heart there occurs the normali zation of intensity of energetic and plastic processes per weight unit of the myocardium This probably provides for the restoration of hemodynamics and contractile capacity of the myocardium at this period At the same time old animals retain at this period the signs of emer gency stage i e minute volume dP/dt max contractility index glycogen content and CP are decreased lactate concentration is increased In other words the phasic changes in heart metabo lism and function are more prolonged and devel

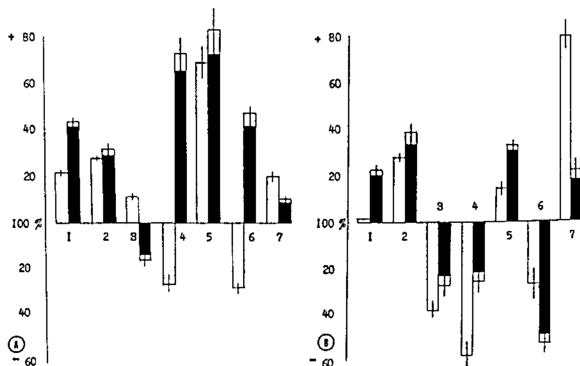


Fig 2 Changes (in per cent) in weight and in indices of carbohydrate and phosphoric metabolism in the hearts of rats of different ages on the fourth to seventh days and on the fourteenth to sixteenth days after aorta coarctation *A* adult rats *B* old rats *White columns* fourth to seventh day after aorta coarctation *Black columns* fourteenth to sixteenth day after aorta coarctation *1* ATP *2* ADP *3* AMP *4* CP *5* IP *6* glycogen *7* lactate

Table V Age peculiarities of changes in energetic metabolism at different periods following aorta coarctation

	Age (months)					
	8 12			*28 32*		
		Days after coarctation			*Days after coarctation*	
Indices	*Initial values* *M ± m†‡*	*4 7* *M ± m*	*14 16* *M ± m*	*Initial values* *M ± m*	*4 7* *M ± m*	*14 16* *M ± m*
ATP (μmoles/G)	1 41 ± 0 03	1 35 ± 0 08	1 51 ± 0 03	1 10 ± 0 05	1 08 ± 0 03	1 24 ± 1 10
ADP (μmoles/G)	0 89 ± 0 02	0 90 ± 0 06	0 83 ± 0 08	0 65 ± 0 04	0 81 ± 0 10	0 8[illegible] ± 0 91
AMP (μmoles/G)	0 71 ± 0 02	0 62 ± 0 05	0 41 ± 0 05*	0 92 ± 0 05	0 54 ± 0 08*	0 6[illegible] ± 0 0[illegible]
CP (mg %)	7 54 ± 0 13	5 43 ± 0 56	9 74 ± 0 89	3 90 ± 0 27	1 81 ± 0 55	2 88 ± 0 [illegible]4
IP (mg %)	21 10 ± 1 20	29 33 ± 2 55*	31 25 ± 1 71	27 60 ± 2 01	29 89 ± 1 35	33 86 ± 1 0[illegible]
Glycogen (mg %)	596 90 ± 20 50	377 24 ± 24 0	847 00 ± 31 00	338 40 ± 27 90	232 00 ± 24 00	145 00 ± 6 00*
Lactate (μmoles/G)	0 78 ± 0 02	0 78 ± 0 02	0 67 ± 0 01	1 17 ± 0 02	1 93 ± 0 03*	1 21 ± 0 01

* = statistically significant differences
†M = mean value
‡m = standard error

oping slowly in old animals, who survived after acute cardiac insufficiency At periods following aorta coarctation, when in adult animals there develop all signs of the relatively stable myocardial hyperfunction stage (fourteenth to sixteenth day), old animals display metabolic and functional shifts which are characteristic of the emergency stage

The analyzed mechanisms of development of cardiac insufficiency in old age are related to certain disturbances in the structures of myocardial cells which can be objectively registered during electron microscopic study As is known the major links of the respiratory chain the processes of oxidative phosphorylation—i e the leading pathways of energy generation within a cell—are situated in mitochondria In old age changes can be observed in the size and shape of

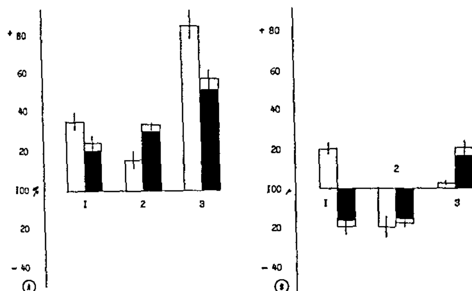


Fig 3 Changes (in per cent) in the content of protein fractions in the hearts of rats of different ages on the fourth to seventh days and on the fourteenth to sixteenth days after aorta coarctation *A* adult rats *B* old rats *White columns* fourth to seventh day after aorta coarctation *Black columns* fourteenth to sixteenth day after aorta coarctation *1* water soluble proteins *2* water insoluble proteins *3* collagen

Table VI Protein fractions in the myocardium of rats of different age and their evaluation at different periods following aorta coarctation

	Age (months)					
	8-12			*28 32*		
		Days after coarctation			*Days after coarctation*	
Protein fractions	*Initial values* $M \pm m$	*4 7* $M \pm m$	*14 16* $M \pm m$	*Initial values* $M \pm m$	*4 7* $M + m$	*14 16* $M \pm m$
Water-soluble proteins (mg./100G)	6000 ± 358	5565 ± 230	4714 ± 609	4862 ± 216	5734 ± 461	3590 ± 200
Water insoluble porteins G /100G)	63 90 ± 1 37	56 40 ± 1 40	59 20 ± 1 89	76 10 ± 1 17	62 00 + 1 18	57 90 ± 1 53
Total collagen (mg /100G)	250 ± 10	416 ± 55	297 ± 25	367 ± 13	428 ± 25	354 ± 18
Labile collagen (mg /100G)	4 00 ± 0 29	4 13 ± 0 46	5 20 ± 0 40	4 65 ± 0 44	5 88 ± 0 47	4 53 ± 0 22

All c lculat o s a e g e per mass f d y f t f e tiss e
Statist ally signific nt d ff ence ($p < 0.05$)

mitochondria their inner structure in the correlation of functionally active and inactive organoids In eight to ten month old rats the prevailing majority of myocardial mitochondria are of relatively the same size having the matrix of moderate electron density and densely packed cristae The majority of mitochondria in the old myocardium have a clarified matrix less compact arrangement of cristae Thus in old age alongside mitochondria of regular size and shape one can find in the perikaryon many of these small organoids with occasional short cristae Separate mitochondria in old myocardium have the increased size are elongated along several sarcomeres and have well distinguishable cristae Residual bodies and the increased number of primary lysosomes can be found here as well (Fig 4) Thus under normal functional conditions the quantity of structurally changed mitochondria is increased in old hearts some of them are dys trophic others have the signs of activation of adaptive mechanisms At the increased load upon the heart (aorta coarctation) more abrupt changes occur in mitochondria of old animals



Fig 4 A Myocardial cells of old animal Intact animal Numerous small mitochondria with occasional short cristae as well as primary lysosomes and residual bodies with lipofuscin are seen in the pericardium of the myocardial cells (original magnification × 10 000) *M* mitochondria *N* nucleus *L* lipofuscin



Fig 4 B Myocardial cells of old animal Cardiac insufficiency Sharp swelling and hydration of mitochondria fragmentation of cristae and outer membrane of myocardial cell mitochondria with signs of cardiac insufficiency (original magnification × 60 000)

Thus on the fourth to seventh day after aorta coarctation the increase in mitochondria mass can be observed both in adult and in old rats Under these conditions the formation of mitochondria is related with activation of plastic processes occurring in the heart and is the expression of major adaptive processes aimed at maintenance of a certain level of energetic provision of intensively working heart The increase of mitochondrial mass in adult animals is gained at the expense of small and medium sized organoids while in old animals one could observe essential numbers of large and gigantic mitochondria (Fig 5) Still, in old animals the quantitative increase of mitochondria after aorta coarctation is less pronounced than in adult animals In addition after aorta coarctation in old animals one can detect in each field of vision the mitochondria with the signs of abrupt swelling vacuolization complete destruction of cristae or with an affinity to osmium condensed matrix and electron dense inclusions With the development of cardiac insuffficiency some mitochondria of old animals are destroyed (Fig 4*B*)

Essential changes in sarcoplasmic reticulum (SPR) of myocardial cells appear in old age and especially at the development of cardiac insufficiency in old animals It is known that the tubular system provides for propagation of intra muscular fiber depolarization, which induces Ca release from SPR vessels resulting in elimination of tropin repression, in actin myosin interaction, and in the development of contraction. The generalized widening of lumina of SPR canaliculi and tubules is constantly detected both in T and L systems It is known that a similar type of changes in SPR myocardial cells is found at a number of pathological states According to Strukov and Paukov [1] such widening of lumina may be of certain adaptive importance The increase of SPR membrane surface may promote the binding and release of calcium In old animals there can be found focal heterogenous changes of SPR in the form of thickening and consolidation of T system canaliculi membranes Often the thickening of T system membranes is found in combination with consolidation of myocardial cell membrane with pronounced reduction in micropinocytic activity (Fig 4*C*) Diffuse widening of SPR canaliculi and tubules develops both in adult and old animals on the fourth to seventh and fourteenth to sixteenth days after aorta coarctation In old animals the widening of canaliculi is less regular with the cyst like widened T system tubule cavities, containing in their lumina the fragments of membranes of cellular organoids At the development of cardiac insufficiency the impairment of architectonics of canaliculi system is observed more frequently in old animals At development of myocardial hyperfunction, the granular reticulum free ribosomes and liposomes can be found more frequently in adult animals than in old ones At hyperfunction numerous ribosomes were detected in adult



Fig 4 C. Myocardial cells of old animal. Cardiac insufficiency Abrupt expansion of T system canaliculi, thickening and consolidation of their membrane and plasmic membrane of myocardial cells. Edema of myofibrils their separation impairment of architectonics and focal homogenization of myofilaments are seen in cytoplasm of the myocardial cell The number of micropinocytotic bubbles in myocardial cell cytoplasm is significantly decreased (original magnification × ?0 000)

animals at outer nuclear membrane at the side of cytoplasm In old age less distinct changes can be found in contractile apparatus of myocardial cells as compared with mitochondria and SPR In old animals against the background of edema and hydration of sarcoplasm one can observe some edema of myofibrils exfoliation of myofilaments less distinct structure of thin and thick filaments Still at the development of cardiac insufficiency significant disturbances appear in contractile apparatus of old animals Sooner than in adult animals there appear foci of chaotic disposition of protofibrillar thick and thin filaments the exfoliation of myofilaments disruption in regularity of disc-strip order and finally homogenization and complete destruction of myofibril to a definite extent (Fig 4C) Fusion of destructive foci destruction of myofibrils along the sarcomere detected by light microscopy techniques are observed in old animals with pronounced manifestations of decompensation Within the same period (fourteenth to sixteenth day after aorta coarctation) the myofibrils of adult animals do not undergo such rough destructive changes they display distinct manifestations of intracellular hypertrophy



Fig 4 D Myocardial cells of old animal. Cardiac insufficiency Distension of space between membranes of intercalated discs (↓) Mitochondria of myocardial cells are swollen with clarified matrix Separation of myofibrils disturbances in disc-strip sequence (original magnification ×20 000) M mitochondria Mf myofibrils

Excitability conduction and synchronization of myocardial contractile capacity are largely related with the state of intercalated discs whose membranes are the combination of myocardial cell plasmic membranes Under conditions of development of cardiac insufficiency the changes

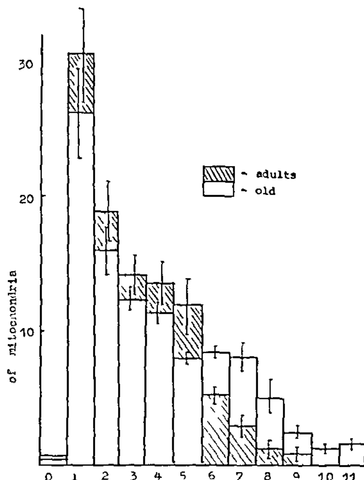


Fig 5 Size distribution of mitochondria in the myocardium of adult and old rats at an emergency stage of hyperfunction

in intercalated discs and distinct expansion of space between their membranes appear in old animals after loading the myocardium Exquisite expansions of intercalated discs along 2500 to 3000 A with the distance between membranes of 1000 to 1500 A (instead of 200 to 300 A in the norm) are found in old animals Inclusions of different electron density can be found within these cyst like expanded spaces of membrane (Fig 4*D*) Thus essential changes in different structures of myocardial cells are observed in old animals already under normal conditions of heart activity and especially after application of functional load

Discussion

The whole complex of the above indices of changes in hemodynamics and myocardial contractile capacity supports the concept of a number of researchers about the development in old age of distinctive physiological insufficiency of myocardium [1] The decline in myocardial contractile capacity related with definite structural and metabolic shifts is the basis for more frequent development of pronounced cardiac insufficiency in old age at loads which are satisfactorily endured at other age periods The development of cardiac insufficiency in a number of old animals is so significant that they die on the second to third day after aorta coarctation with the increasing manifestations of blood congestion in greater and lesser circulation circles Still the fact must be stressed that all these principles cannot be applied indiscriminately to every old animal We found that in one group of them initial parameters of hemodynamics and peculiarities of hemodynamic reactions upon loads do not differ much from the shifts observed in adult animal This concept is in accord with the results of a study of myocardial metabolism which show that in some animals the tissue respiration oxidative phosphorylation, adenyl nucleotide content and metabolism do not differ significantly from the same indices of adult animals Consequently the age related changes of the cardiovascular system are heterogenous and this determines a wide quantitative and qualitative range of cardiac reactions upon increased load in old age In other words while stressing quite reasonably the development of distinctive cardiac insufficiency in the majority of old individuals one should take into consideration a group of them with a relatively high working capacity of the myocardium

To understand the mechanisms of development of cardiac insufficiency in old age it is necessary to analyze age related changes in (*a*) regulation of myocardial contractile capacity, (*b*) mechanisms of achievement of systole and diastole (*c*) plastic provision of myocardial structure which is reached owing to protein biosynthesis

The mechanism of direct inotropic effect of the sympathetic nervous system upon heart suffers in old age In an old heart we found a decrease of norepinephrine content and a rise of thresholds of inotropic effects upon the heart at the stimulation of stellate ganglion The fact is interesting that the transmitter content in atria and right ventricle declines more abruptly as compared with that of the left ventricle These data are interesting in connection with the supposition that many of the regulatory mechanisms are represented more widely in the right ventricle due to its immediate hemodynamic mobilization at loading Also important is the fact that at the application of load producing the hyperfunction

the norepinephrine content declines significantly in all parts of the adult heart on the fourteenth to sixteenth day after aorta coarctation Insignificant decline of norepinephrine content is observed in the left ventricle of old animals whereas it is increased in the right ventricle and atria It may be supposed that the regulatory mechanism of norepinephrine involvement in myocardial metabolism suffers in old animals and this limits the mobilization capacity of energetic processes and promotes the development of cardiac insufficiency Verkhratsky[27] showed the weakening of norepinephrine synthesis in the sympathetic nervous terminals decline in the intensity of transmitter uptake a fall in the quantity of β adrenoreceptors and irregular alterations of catecholamine transferase and monoamine oxidase activity in the heart All this results in changes in transmitter metabolism in weakening of adrenergic regulation of heart activity and in changes of the contractile capacity of the myocardium

The weakening of positive nervous inotropic influences upon the myocardium in old age promotes the role of local mechanisms of autoregulation in adaptation of heart to load

It is known that the myocardial contractile capacity is controlled by a number of mechanisms a major importance being the mechanism of Frank Starling (length-tension ratio) and direct inotropism which is closely related with adrenergic influences upon the heart The mechanism of Frank Starling suffers greatly during aging and this limits the adaptive capacities of the heart This is related with the decline in elasticity of muscle fibers per se with the increase of poorly elastic connective tissue with the appearance of the atrophied and hypertrophied muscle fibers and with changes in bonds within the actomyosin complex Therefore the myocardium develops the lesser tension reacting on one and the same distension In this connection we would like to remind the reader about the rise in the quantity of residual blood in the heart cavities of elderly and old subjects Thus both homometric and heterometric regulatory mechanisms of heart contractile capacity suffer in old age promoting the development of cardiac insufficiency at the increase of load upon the myocardium

In accordance with the modern concepts the contraction of myocardial fiber is determined by the successive involvement of the following mechanisms depolarization Na influx and K efflux from cardiac histocyte K efflux from SPR and its association with tropin lifting of tropin repression actin-myosin interaction activation of adenosine triphosphatase activity of myosin splitting of ATP and contraction of myofibrils During aging the content of intracellular Na is increased and the content of K decreased and the amplitude of muscle fiber action potential declines and its duration tends to increase [9] It is known that the depolarization wave spreading over the outer membrane of muscular cell displaces Ca Z ions from SPR into myofibrils where they being bound by Ca reactive protein eliminate its inhibiting action upon tropomyosin and make the binding of actin with myosin possible [3, 3] The rate of reverse binding of Ca by SPR determines the course of diastole The change in K /Na relationship influences the state of the calcium-sodium pump It may be assumed that changes in SPR and disturbances in the calcium pump effect significantly the myocardial contractile capacity and diastolic relaxation of the heart in old age The heterogenous changes in SPR and the thickening and induration of T system canaliculi are observed in old animals SPR power per unit of cell mass declines during aging The increase of sarcolemma-vessel contacts which provide for the optimal rate of Ca efflux and influx into SPR and optimal conditions for achievement of systole and diastole is less pronounced at the increased load upon an old heart

Our electron microscopic data showed that structural changes in cardiac histocyte contractile apparatus in old animals are less pronounced than in mitochondria and SPR Still rough disturbances in contractile apparatus up to chaotic changes of thick and thin filaments of protofibrils and homogenization and complete destruction of myofibrils appear in old animals after the application of load under conditions of the development of cardiac insufficiency Synchronization of activity of separate myocardial cells is of significant importance in the provision of heart contractile capacity The synchronization is largely determined by the state of intercalated discs—i e the point of contact of separate myocardial cells Upon application of load a distinct expansion of intercalated discs (with a three to fourfold increase of distance between them) is observed in old animals This results in

difficulties in conduction of excitation between separate cells, impairment of synchronization of their contraction, prolongation of systolic phases and decline in cardiac contractile capacity As is known, the synchronization of processes of contraction of separate myocardial fibers is regulated by adrenergic nervous influences Weakening of adrenergic influences upon the heart in old age aggravates the impairment of inotropic mechanisms as well as the synchronization of contraction of myocardial fibers

There are a number of molecular mechanisms which limit the function of heart contractile apparatus in old age and promote the development of cardiac insufficiency One of them is the impairment of properties of myocardial contractile proteins the change in actin-myosin bond Lohman[33] showed that the viscosity of the actomyosin complex taken from a cow s heart alters under ATP effect to a lesser extent than that taken from a calf's heart According to Khilko[34] the correlation of sulfhydryl and disulfide groups changes significantly in myosin of old animals We found changes in contractility index which according to Siegel and Sonnenblick[35] is determined by the rate of interaction of active centers of actin with myosin fibers, by the formation of bonds between them Impairment of these bonds, changes in formation and liquidation rate, reduction of myocardial contractile capacity in old age and finally quantitative decrease of myofibrillar proteins, observed by us, may be a reason for the development of cardiac insufficiency

Significant shifts appear in old age both within the contractile apparatus at the stage of conversion of chemical energy into mechanical energy and in different links of energy generation in the heart Significant changes in energetic processes (decrease of ATP CP and glycogen contents accumulation of lactate, etc) appear as early as under normal conditions The contractile function of the myocardium is maintained to a great measure, owing to mobilization of a number of adaptive mechanisms—i e increase of oxidation and phosphorylation coupling, rise of glycolysis intensity, increase of activity of a number of glycolytic and respiratory enzymes [36]

On the fourth to seventh days and fourteenth to sixteenth days after aorta coarctation pronounced changes in energetic metabolism appear in old animals It is noteworthy that ATP content is not changed significantly and this is in accord with earlier reports[37-40] describing insignificant changes in ATP content at cardiac insufficiency Obviously, it is not this mechanism which limits the functional capacities of the heart at this period At the same time, after aorta coarctation CP content is decreased twofold in an old heart as compared with an adult heart Taking the existing suppositions[41] about the role of CP in transfer of energy from mitochondria to contractile proteins of myofibrils as a basis one can speculate that the decline in CP content plays an essential role in the possible mechanism of development of cardiac insufficiency Account should also be taken of a decline in glycogen content and more than a fourfold increase of lactate content in the heart of old rats Significant accumulation of lactate in an old heart may lead to the shifts in medial pH thus affecting the myocardial contractile capacity Insufficient energetic provision of heart activity in old age is related with the shifts in the structure of mitochondria The mitochondria with altered size and shape with the impaired inner structure can be found in old age already under normal conditions of heart activity One of the most important adaptive mechanisms of the heart during the process of hypertrophy is related to the formation of mitochondria After aorta coarctation the quantitative increase of mitochondria is less pronounced in old animals than in adult animals

It should be noted that in separate organoids of myocardial cells in contractile proteins the shifts at different stages of energy generation which determine the development of cardiac insufficiency are related with primary mechanisms observed in the genetic apparatus in the processes of protein biosynthesis Limitation of potential possibilities of biosynthetic systems and shifts in regulation of genetic apparatus lead to a decreased activation of newly formed protein in response to decreased load upon an old heart We found no increase in heart weight of old animals on the fourth to seventh and on the fourteenth to sixteenth days after aorta coarctation only an insignificant increase in content of all studied protein fractions could be observed In adult animals these shifts were rough The quantitative increase of ribosomes and polysomes is less pronounced in old animals after an increase of load upon the heart The limitation of potential possibilities of protein biosynthesis in old age leads to a less pronounced hypertrophy of

myocardial cells at hyperfunction In old age as early as under normal conditions the potential possibilities of biosynthetic systems are mobilized in a great measure and this limits the range of rejuvenation of major structures of the myocardial cell which are necessary to perform substantial work

Owing to changes in the genetic apparatus and in protein biosynthesis a number of myocardial cells die in old age while the rest have to take the increased load under normal conditions and many of them get hypertrophied All this creates the situation in old age at which the load upon the heart often exceeds its capacity to perform work, hence the development of cardiac insufficiency

Thus the development of cardiac insufficiency in old age is conditioned by a number of essential shifts in heart metabolism and function in their regulation (weakening of adrenergic nervous influences upon the heart changes in length-tension ratio in the contractile act shifts in SPR structure and function changes in properties of contractile proteins shifts in the metabolism of macroergic phosphoric compounds and potential capacities of the heart genetic apparatus)

Depending on the conditions of load upon the heart this or that link in the provision of contractile act (which is altered with age) can become a limiting factor Thus for instance a short term heavy load upon the myocardium of leading importance are the shifts in adrenergic regulatory mechanisms calcium pump etc while at long term load of ever growing significance are the primary changes in protein biosynthesis system in the plastic provision of heart function

REFERENCES

1 Beznak, M. J Cardiac output in rats during the development of cardiac hypertrophy Circ Res 632 207 1958
2 Kogan A Kh. New simple technique of dosed coarctation of renal and other arteries of small laboratory animals in chronic experiment Bull. Eksper i Med 1 112 1961 (in Russian)
3 Fegler G Measurement of cardiac output in anesthetised animals by a thermodilution method Q J Exp Physiol 39 1o3 1954
4 Gurevich, M I Bernstein S A and Golov D A Measurement of cardiac output by a thermodilution method Fiziol. Zh SSSR 3 350 196o (in Russian)
5 Veragut U P and Kravenbuhl H P Estimation and quantification of myocardial contractility in the closed chest dog Cardiologia (Basel) 47 2 96 196o
6 Karpman V L Phase analysis of cardiac activity Meditsina Publishing House Moscow 1965 (in Russian)
7 Stransky Z Determination of adenine nucleotides by paper electrophoresis J Chromatogr 10 4 1963
8 Fiske C and Subbarow J Nature of inorganic phosphate in voluntary muscle Science 65 401 1927
9 Lowry O H and Lopez J A Determination of inorganic phosphate in the presence of labelling ester J Bi l Chem 162 421 1946
10 Skulachev V P Correlation of oxidation and phosphorylation in respiratory chain Izd AN SSSR Moscow 1962 (in Russian)
11 Morris D L Quantitative determination of carbohydrates with Dreywood s Anthrone Reagent Science 107 254 1948
12 Kuft J W., and Perlgweig W The fluorescent condensation product of N methylnicotinamide and acetone A sensitive method for the determination of N methylnicotinamide in urine J Biol Chem 167 1 157 1947
13 Cavalini, D., and Frontali N Quantitative determination of ketoacids by paper partition chromatography Biochem Biophys. Acta 13 439 1954
14 Dische Z and Laszlo D Uber eine neue kolozimetrische Bestimmungsmethode der Milchsäure im Blute Biochem Ztschr 187 344 1927
15 Lowry O Rosenbrouch, N., Farr A and Randall R. Protein measurement with the Folin phenol reagent J Biol Chem 193 255 1951
16 Weibel, E R., Kistler G S and Scherle W F Practical stereological methods for morphometric cytology J Cell Biol 30 23 1966
17 Meerson F Z Hyperfunction Hypertrophy Cardiac insufficiency Meditsina Publishing House Moscow 1968—Narod i zdorovje Publishing House Berlin (GDR) 1968 (in Russian)
18 Meerson F Z and Pshennikova M G The effect of myocardial hypertrophy on the contractile function Bull Eksper Biol i Med 1 36 1965 (in Russian)
19 Atkinson D E The energy charg of the adenylate pool as a regulatory parameter Interaction with feedback modifiers Biochemistry (Wash.) 7 4030 1968
20 Strukov A I and Paukov B S Modern ideas of the functional morphology of contractile myocardium Arkhiv Patol 4 3, 1969 (in Russian)
21 Strajesko N D On peculiarities of manifestation and course of diseases in the aged in Old age 19 1940 Kiev (in Russian)
22 Wezler K and Boger A Wachstum und Altern in Kreislauf Klin Wschr 15 257 1936
23 Morpurgo H Aspetti fisiopatologici del onore senile Giorn Gerontol 6 648 1958
24 Burger M Altern und Kranheit als Problem Biomorphose 4 Aufl., VEB G Thieme Leipzig 1960
25 Cherkassky L P and Polinskaya V I Age peculiarities of phase structure of left ventricle systole in rabbit heart Fiziol. Zh. AN Ukr SSR 3 304 1974 (in Ukrainian)
26 Meerson F Z Kapelko V I and Radzievsky S A Correlation of contractile function and metabolism of left ventricle and right heart Kardiologia 2 146 1968 (in Russian)
27 Verkhratsky N S Characteristics of catecholamine metabolism during aging in Ninth International Congress on Gerontology Reports Kiev (USSR) 1 100 19 2
28 Tokar A V Heart volume and quantity of residual blood in its cavities in relation to age a d level of arterial pressure Kardiologia 3 112 1973 (in Russian)
29 Frolkis V V Regulation adaptation and aging Nauka Publishing House Leningrad 1970 (in Russian)
30 Ebachi S and Lipmann F Adenosine triphosphate linked concentration of calcium ions in particulate frac

tion of rabbit muscle J Cell Biol 14 389 1962
31 Hasselbach W Relaxing factor and relaxation of muscle Progr Biophys Mol Biol 14 167 1964
32 Weber A Herz R and Reiss I Regulation of myofibrillar activity by calcium Proc R Soc Med 160 489 1964
33 Lohman M Cited after M Burger Altern und Krankheit als Problem Biomorphose Leipzig 1960
34 Khilko O KH Effect of process of aging on properties of myogen thiogroups *in* Ninth International Congress on Gerontology Abstracts Kiev (USSR) 3 408 1972
35 Siegel J H and Sonnenblick E H Isometric time-tension relationships as an index of myocardial contractility Circ Res 12 6 597 1963
36 Frolkis V V and Bogatskaya L N Age peculiarities of energetic metabolism of heart Kardiologia 2 66 1967 (in Russian)
37 Minton P R Zoll P M and Norman L R Level of phosphate compounds in experimental cardiac hypertrophy Circ Res 8 924 1960
38 Wollenberger A Kleitke B and Raabe G Some metabolic characteristics of mitochondria from chronically overloaded hypertrophied hearts Exp Molec Pathol 2 251 1963
39 Pool P E Spann J F and Sonnenblick E H Myocardial high energy phosphate stores in cardiac hypertrophy and heart failure Circ Res 21 365 196
40 Braunwald E Ross J Jr and Sonnenblick H Mechanisms of contraction of the normal and failing heart, Boston 1968
41 Saks V A Chernousova G B Voronkov J Smirnov V N and Chasov E I Study of energy transport mechanism in myocardial cells Circ Res 35 3, 109 1974

Early changes ın contractılıty and coronary blood flow ın the normal areas of the ıschemıc porcıne heart

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Roger Holland B S E E
Harold Brooks M D
Chıcago Ill

The nature of the ıschemıc process and the response of the remaınıng normally perfused myocardıum are subjects of ıntense current ınterest and ınvestıgatıon Mechanıcal electrı cal[5] bıochemıcal[8 1] and morphologıc de rangements ın an area of myocardıum followıng cessatıon of ıts normal coronary artery blood flow have been well characterızed

A major consequence of loss of functıon of the ıschemıc or ınfarcted myocardıum ıs that the remaınıng nonıschemıc tıssue must be called upon to perform proportıonately more work ıf adequate levels of cardıac output and blood pres sure are to be maıntaıned While an actual ıncrease ın contractıle force development has not prevıously been demonstrated dırectly several studıes have shown that the dıstant nonıschemıc myocardıum does respond to acute coronary artery occlusıons ın the ıntact heart Changes ın the levels of tıssue catecholamınes [2] adenosıne trıphosphate (ATP) cyclıc adenosıne mono phosphate (AMP) and electrolytes as well as ıncreases ın oxygen consumptıon coronary blood flow and altered venous effluent have all been shown to occur ın thıs nonıschemıc area

The purpose of thıs ınvestıgatıon was to char acterıze our prevıous casual observatıons of a consıstent pattern of mechanıcal and electrıcal change ın areas of the left ventrıcle located outsıde an acutely ıschemıc regıon of the other wıse ıntact porcıne heart

Methods

The pıg was chosen as the experımental model for the study Several comparatıve anımal studıes have shown sımılarıtıes between porcıne and human gross coronary archıtecture [9] and collater al cırculatıon Recent studıes ın our laboratory have extended these demonstratıng sımılarıtıes ın arterıal dıstrıbutıon to regıonal ventrıcular myocardıum and supply of SA and A V nodal tıssue

Experıments were performed ın 20 healthy condıtıoned domestıc pıgs of both sexes rangıng ın weıght from 33 to 54 kılograms After ınductıon of anesthesıa wıth a small ıntravenous ınjectıon of thıopental the anımals were anesthetızed wıth an ıntravenous ınfusıon of a warmed solutıon of alpha chloralose (60 mg per kılogram) Supple mentary doses of chloralose were gıven durıng the thoracotomy and ınstrumentatıon to maıntaın a relatıvely unıform state of anesthesıa However no anesthetıc agent was gıven followıng the measurement of the ınıtıal control state Respıra tıon was maıntaıned by a Harvard Volume Respı rator regulated to maıntaın an arterıal pH of 7 45 ± 0 05 throughout the experıment The pump was connected to a tracheostomy tube and supplemental oxygen was admınıstered to maın taın arterıal oxygen saturatıon at 95 per cent throughout the study The heart was exposed by

From The Hecht Experım nt l H modynamıcs Lab rat ry D p rt ment f Medı ıne—Card ol gy The U ers ty f Ch cago Prıtzker School f Medıcıne Chı ag Ill

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tion of rabbit muscle J Cell Biol 14 389 1962
31 Hasselbach W Relaxing factor and relaxation of muscle Progr Biophys Mol Biol 14 167 1964
32 Weber A Herz R and Reiss I Regulation of myofibrillar activity by calcium Proc R Soc Med 160 489 1964
33 Lohman M Cited after M Burger Altern und Krankheit als Problem Biomorphose Leipzig 1960
34 Khilko O KH Effect of process of aging on properties of myogen thiogroups *in* Ninth International Congress on Gerontology Abstracts Kiev (USSR) 3 408 1972
35 Siegel J H and Sonnenblick E H Isometric time-tension relationships as an index of myocardial contractility Circ Res 12 6 597 1963
36 Frolkis V V and Bogatskaya L N Age peculiarities of energetic metabolism of heart Kardiologia 2 66 1967 (in Russian)
37 Minton P R Zoll P M and Norman L R Level of phosphate compounds in experimental cardiac hypertrophy Circ Res 8 924 1960
38 Wollenberger A Kleitke B and Raabe G Some metabolic characteristics of mitochondria from chronically overloaded hypertrophied hearts Exp Molec Pathol 2 251 1963
39 Pool P E Spann J F and Sonnenblick E H Myocardial high energy phosphate stores in cardiac hypertrophy and heart failure Circ Res 21 365 1967
40 Braunwald E Ross J Jr and Sonnenblick H Mechanisms of contraction of the normal and failing heart Boston 1968
41 Saks V A Chernousova G B Voronkov J Smirnov V N and Chasov E I Study of energy transport mechanism in myocardial cells Circ Res 35 3 109 1974

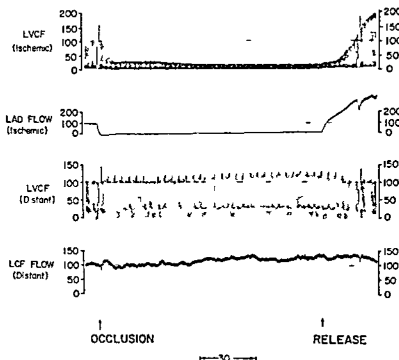


Fig 2 Recording of ischemic (above) and distant (below) myocardial contractile force and coronary blood flow responses during transient ischemia (1?0 sec) Note the characteristic augmentation (above dashed line) of contractile force and coronary blood flow in the distant area All scale units are per cent change from control

circuit from the right carotid artery For this procedure the animals were anticoagulated with 10 000 units of heparin intravenously The proximal left circumflex artery was cannulated from the epicardial surface with a polyethylene catheter (Angiocath Deseret Co Sandy Utah) Flow was immediately re established via an external perfusing circuit supplied by the right carotid artery The cannulation procedure took less than 60 seconds to perform and in each case an unequivocal and reproducible increase in contractile force in the distant area had been obtained just prior to cannulation The system was allowed to perfuse via the external circuit uninterrupted for 10 to 15 minutes following cannulation and before the anterior descending artery was again occluded The presence of perivascular neural fibers in the adventitia of the anterior descending and circumflex arteries was confirmed in these animals post mortem Sections of these arteries were obtained fixed in the usual manner with 10 per cent neutralized formalin and stained with Kluver Bodian or hemotoxylin and eosin stains for the demonstration of nerve fibers Statistical

Table I Cumulative data and significance of contractile changes in ischemic and distant areas of myocardium following occlusion*

	Change (%)	*Occlusions*	*Animals*	*Significance†*
Regional contraction				
LVCF (ischemic)	−81 4 ± 1 4	57	15	$p < 0.001$
LVCF (distant)	+1?6 ± 0 9	57	15	$p < 0.001$
Coronary blood flow				
Ischemic	−100	17	6	$p < 0.001$
Distant	+16 8 ± 4 5	17	6	p < 0 00?

Mean ± S E M
†Paired t test (25)

analysis was carried out with the paired t test [25]

Results

The mechanical responses of the ischemic and distant nonischemic areas of the left ventricle following a transient left anterior descending occlusion in a representative experiment are illustrated in Fig 2 Within seconds following the cessation of anterior descending blood flow there occurs a rapid decline in contraction of the

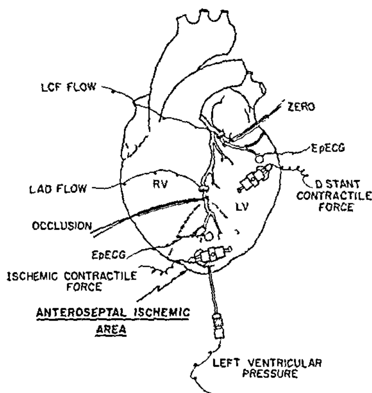


Fig 1 Schema of the experimental design indicating the two regions of study the anteroseptal ischemic area supplied by the anterior descending artery (LAD) and the distant nonischemic area supplied by the left circumflex artery (LCF) EpECG = epicardial surface electrode LV = left ventricle RV = right ventricle

a midsternal thoracotomy pericardiotomy was performed, and a pericardial cradle was created to support the exposed heart

Two regions of the myocardium were selected for study—each supplied by separate branches of the coronary system the low anteroseptal area supplied by the distal left anterior descending coronary artery was designated the ischemic area and the high lateral left ventricular free wall supplied by the left circumflex artery was designated the nonischemic area Three parameters were used to assess the dynamic responsiveness of each area and these are shown schematically in Fig 1 an isometric strain gauge of the Walton Brody type a cuff probe electromagnetic flow meter on the proximal portion of the artery supplying the respective region, and an epicardial surface electrocardiogram (ECG) electrode The isometric strain gauge arch (John Warren Department of Pharmacology, University of South Carolina) was sutured firmly to the myocardium, anchored to and oriented in series with outer wall myocardial fibers and stretched to 40 per cent over initial length Previous studies have shown this to be the optimal amount for maximally recording mechanical changes in the subjacent myocardium [3] Coronary arterial blood flow to both regions was measured with a gated sinewave electromagnetic flowmeter (Biotronex Laboratories, Silver Springs Md) The cuff probe was placed around the artery with minimal dissection or stripping of the artery s adventitia to avoid possible damage of perivascular nerves A silk ligature (00) was placed around each coronary artery immediately distal to the probe and reversible occlusion of these ligatures was achieved by temporarily tightening the silk snare with a polyethylene collar Occlusions were of approximately 120 seconds' duration Epicardial surface potentials were measured by an atraumatic, firmly attaching electrode [4] The electrode was positioned over the myocardium supplied by each of the two myocardial arteries selected and fixed to the epicardial surface with a new tissue bonding agent Eastman 910 (Eastman Chemical Division Kingsport Tenn) This permitted continuous monitoring of the epicardial ECG with negligible baseline shift often quite difficult to obtain with wick electrodes The electrical signals were recorded with a Bioelectric Amplifier (No 8811A, Hewlett Packard Co Waltham Mass) having a high and low frequency response of 0 15 and 300 Hz (−3db), respectively

Whole ventricular dynamics were measured immediately before and 120 seconds following coronary occlusion in 11 animals heart rate (HR) the time derivative of left ventricular pressure (LV dP/dt) and left ventricular pressure were continuously monitored Pressure determinations were made through a 6 inch Teflon 16T gauge intracardiac needle placed in the left ventricular cavity at the apex and connected to a Statham P23Db pressure transducer The pressure signal was differentiated electronically to obtain LV dP/dt All parameters were recorded on an eight channel direct ink recorder and FM magnetic tape recorder (Hewlett Packard Co Waltham Mass)

The initial series of experiments involved 13 animals (Group I) with force gauges epicardial electrodes and electromagnetic cuff probes in the ischemic and distant areas In an additional subset of experiments involving three animals (Group II) the left circumflex artery was transected and externally perfused via an external

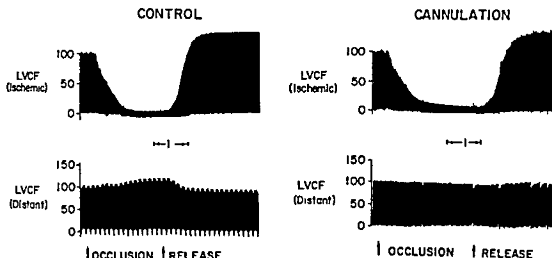


Fig 4 Recordings of ischemic and distant contractile activity before (above) and after (below) cannulation procedure The augmented contractile response in the distant area is obliterated by transection of the left circumflex artery and subsequent cannulation Scale units are per cent change from control

activity and coronary blood flow in the distant nonischemic area increased significantly A rise in coronary blood flow though frequently observed in association with the rise in contractile activity was not always apparent nor did it correlate well with the magnitude of the contractile change ($r = 0.22$) On rare occasions blood flow remained unchanged or actually decreased in the distant area

Changes in whole ventricular dynamics shown in Table II were relatively small at this early stage of ischemia (60 seconds post occlusion) Although all parameters measured showed statistically significant changes at this time the hemodynamic importance of these changes as regards either the initiation of or contribution to the observed increase in distant contractile activity is not known Changes in heart rate and left ventricular end diastolic pressure were slight and correlated poorly ($r = 0.36$ and $r = 0.55$) with the increase in distant contractile activity

The possibility that a neural effect was operative in initiating the increased contractile activity in the distant nonischemic myocardium was investigated with the Group II series in which the left circumflex artery and any of its surrounding perivascular neural fibers were transected the artery cannulated and perfused via an external circuit from the carotid artery Recordings from a representative experiment showing the response of the two areas to coronary occlusion before and after the cannulation procedure are illustrated in Fig 4 Cumulative data from this Group are presented in Fig 5 The expected increase in distant contractile activity recorded repeatedly in each of the animals just 15 to 20 minutes

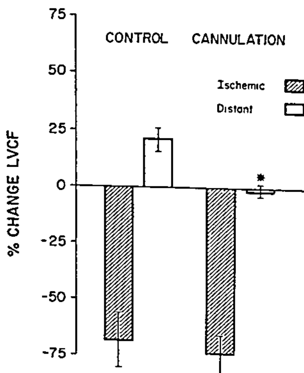


Fig 5 Cumulative data from animals which underwent cannulation procedure Increase in contractile activity of distant area is essentially obliterated ($p < 0.05$) however no change in the degree of contractile depression in the ischemic area was observed

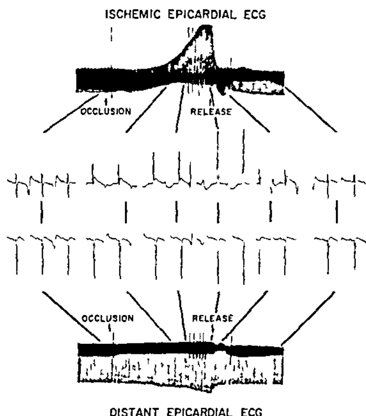


Fig 3 Changes in epicardial surface electrograms recorded from ischemic (above) and distant (below) areas during transient ischemia (120 sec) Ischemic complexes show TQ ST segment elevation and dramatic increases in the R wave Distant complexes show very slight TQ ST segment depression and increases in S wave voltage

ischemic area to minimal levels Within the same short period of time contractile activity in the distant area increases by 5 to 7 per cent above control levels As the duration of the ischemia increases (usually within the following 30 seconds) the distant contractile response reaches a plateau which is 10 to 15 per cent greater than control Here the level of contractile activity is maintained until release of the coronary artery occlusion With release and the re establishment of flow contractile activity in the ischemic area returns toward control levels following a brief characteristic post occlusion overshoot response corresponding to the coronary blood flow hyperemia The distant contractile activity however quickly returns to control levels following the release

The surface electrical responses of the ischemic and distant areas following occlusion are illustrated in Fig 3 The electrogram changes recorded over the ischemic segment of the intact porcine heart are characteristic and reproducible

Table II Changes in whole ventricular dynamic following occlusion (23 occlusions in 11 animal)

Animal No	HR (b p m)	LVSP (mm Hg)	LVEDP (mm Hg)	LV dP dt (mm Hg sec)
1	2	–7	2 5	–680
2	8	–2	2 5	0
	2	–3	2 5	–680
3	5	–2	0 5	–80
4	5	–8	1 5	–170
	–6	–2	3 0	–200
5	6	–6	0 0	–280
6	3	–4	2 0	–320
	4	–4	1 0	–240
	4	–6	1 0	–80
	4	–5	2 5	–200
	5	–12	1 0	–160
7	0	0	1 0	–60
	2	–2	1 5	–180
8	1	–32	0 0	–340
	12	–8	3 0	–65
	–4	–10	1 0	–80
	0	–3	1 5	–65
9	3	–11	0 0	–
	0	–11	0 5	–
	2	–14	1 0	–
10	0	–8	1 5	–360
11	0	–6	1 0	–258
Means	2 5	–7 2	+1 4	–224
S E M	±0 8	±1 4	±0 2	±42
T	3 13	5 14	7 00	5 33

Paired t test (25) $p < 0.005$
Abbreviations HR = heart rate LVSP = left ventricular systolic pressure LVEDP = left ventricular end-diastolic pressure LV dP dt = time derivative of left ventricular pressure

and have been previously described by the authors in detail [6, 8] In the figure they can be seen as a slight initial decrease in R wave height within 5 seconds after the occlusion followed in approximately 50 seconds by a dramatic and progressive rise in R wave voltage with evidence of a concomitant widening in the QRS In addition to this biphasic alteration in the R wave voltage a steady and progressive elevation in the ST segment is observed In the distant area slight TQ ST segment depressions on the order of less than 1 0 mv are observable In addition small but significant variations in the QRS complex and T wave uniformly occurred and consisted of a slight decrease in R wave amplitude and an increase in S wave amplitude

Cumulative data for all occlusions in the 10 animals of Group I along with a t test analysis of each parameter are presented in Table I Following coronary artery occlusion contractile

the peripheral vasodilation that occurs following acute experimental coronary artery occlusion[32,33]

With such a signal arriving in the distant area several different mechanisms might be available to translate it into increased contractile force development First it might act directly upon the myocardial cell membrane to increase either cyclic AMP production and/or calcium uptake by the distant cells Recently Polimeni and Al Zadir[13] have shown that the calcium content of the nonischemic region increases by some 25 per cent in the rat heart following occlusion of the left anterior descending coronary artery These changes were observed 24 hours following occlusion and it is not known whether or not they can be demonstrated to occur within seconds following coronary occlusion as did the contractile changes we observed

Second the signal might act to release intramyocardial norepinephrine stores[12, 13] thus resulting in augmented contractile force development Third the signals might act not on the myocardial cells directly but on those blood vessels supplying this region Regional vasodilation and increased coronary blood inflow might then result in the ability of that area to increase its contractile force development A number of investigators have shown[3, 5] that coronary blood flow may very well be an independent determinant of cardiac function Presumably such a coronary flow–contractile force mechanism might depend on the ability of increased coronary blood flow to increase oxygen and substrate delivery and to permit faster removal of certain inhibitory metabolic by products (e g hydrogen ion)[38] One of these components or functions of coronary blood flow might limit maximal contractile force development in the myocardium

It is conceivable that the increase in distant activity is initiated by stimulation of aortic baroreceptors and that this results in the enhancement of sympathetic activity in the distant region However it seems unlikely that such a small drop in left ventricular systolic pressure (7 mm Hg) observed during the first 60 seconds would have been of sufficient magnitude to activate the baroreceptors In many animals no measurable drop in pressure occurred despite substantial increases in distant activity In addition the very slight changes seen in heart rate gave little indication that substantial increases in systemic sympathetic activity have occurred and are responsible for the increased distant contractile activity

Finally the question of artifact must be addressed Is it likely that alterations in the distant strain gauge are mechanically transmitted via changes occurring in the ischemic area? The demonstrated loss of the distant segment s response following transection and cannulation without corresponding changes in the ischemic segment s response would seem to exclude this possibility from further consideration

The electrical changes recorded by electrodes overlying the ischemic area have been discussed before[6, 3] and are generally believed to be due to the progressive leakage of potassium out of the injured cells and into the surrounding extracellular space[6] The changes seen in the distant nonischemic area are only slight to begin with and appear somewhat attenuated but not obliterated by the cannulation procedure We would conclude that the observed reductions in R wave and increases in S wave amplitude as well as the slight TQ ST segment depression seen in electrodes overlying the distant region are primarily the result of the reciprocal vectorial forces evolving in the ischemic area

We conclude that a complex relationship exists between the ischemic and the nonischemic but potentially endangered myocardium The augmented contractile response of distant myocardium during coronary artery occlusion demonstrated herein with the porcine heart may comprise a direct mechanism for the preservation of near normal whole ventricular dynamics following substantial loss of functional myocardial mass From a teleologic and clinical viewpoint the presence of a rapidly acting reflex mechanism which can counteract an immediate loss of functioning myocardial mass by augmenting contractile force in a distant area is certainly desirable if an adequate level of cardiac performance is to be maintained following the acute insult of myocardial infarction

Summary

The regional responses of normal myocardium distant from an ischemic area were studied during acute anterior descending occlusion in the open chest chloralose anesthetized pig Three markers of regional response in both normal and ischemic

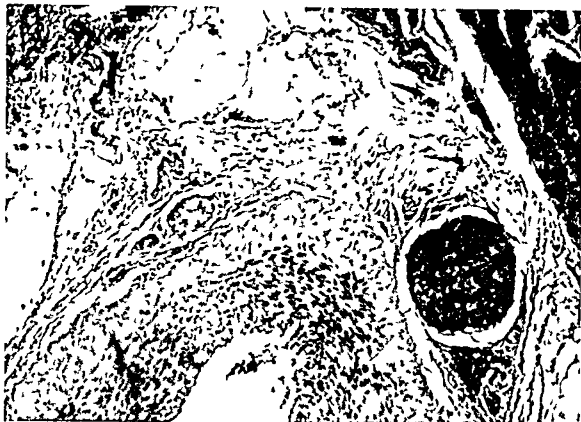


Fig 6 Photomicrography (hematoxylin and eosin) of a section of the circumflex artery and its surrounding adventitia is shown Nerve fibers are present in the perivascular connective tissue

previously, was now essentially obliterated The changes in left ventricular dP/dt and end diastolic pressure occurred to the same levels as they had before transection and cannulation of the artery The normal series of QRS alterations in the distant area were somewhat attenuated but the development of the slight TQ ST segment depression was repeated

In Fig 6 a photomicrograph of a section of the circumflex artery and its surrounding adventitia is shown Prominent perivascular nerves such as those illustrated were seen in all segments examined

Discussion

This study indicates that a significant augmentation of contractile force development occurs in the distant nonischemic myocardium of the intact porcine heart within seconds after acute anterior descending artery occlusion This increase in contractile activity is usually associated with a concomitant increase in left circumflex coronary blood inflow to the distant region Furthermore, transection of the circumflex artery with immediate re establishment of flow uniformly obliterates the distant response without any apparent alteration in whole ventricular dynamics These observations along with the rich perivascular nerve supply seen in the histological sections suggests that a neurovascular mechanism may be responsible for the rapid evolution of increased contractile activity in the nonischemic myocardium

Previous experiments by Aviado and Schmidt[27] have suggested that ischemia or asynchronous contraction of the left ventricle gives rise to a neural arc originating within the ischemic area Impulses arising from hypothetical stretch receptors sensing the asynergic contraction of the ischemic area would travel via afferent fibers to the regional autonomic ganglion They would be referred centrally and then back to the distant nonischemic area via an efferent network present in the adventitial layer of the coronary vessels[28] Previous histologic studies have disclosed an abundance of sensory receptors in the myocardium[29] and coronary vessels[30] In 1867, with the first description of the Bezold Jarisch reflex it was hypothesized that chemoreceptors were present in the myocardium which could be stimulated by a rapid accumulation of adenosine in the ischemic tissue and referred via parasympathetic efferents in the vagus nerve[28,31] More recently reflex mechanisms have been sought to explain

Nakano J Effect of changes in coronary arterial blood flow on the myocardial contractile force Jap Heart J 7 ı8, 1966
Fisher V J Jr Martino R A Harris R S and Kavaler F Coronary flow as an independent determinant of myocardial contractile force Am J Physiol 217 11?ı 1969
Opie L. H Coronary flow rate and perfusion pressure as determinants of mechanical function and oxidative metabolism of isolated perfused rat heart J Physiol (Lond) 180 5?9 196?

37 Katz A M Effects of ischemia on the contractile processes of heart muscle Am J Cardiol 32 456 1973
38 Gelet T R Altschuld R A and Weissler A M Effects of acidosis on the performance and metabolism of the anoxic heart Circulation Suppl IV 60 1969
39 Ekmekci A Toyoshima H Kwoczynski J K Nagaya T and Prinzmetal M Angina pectoris V Giant R and receding S wave in myocardial ischemia and certain nonischemic conditions Am J Cardiol 7 521 1961

areas were used surface ECG electrode a force gauge in series with left ventricular outer wall fibers and coronary blood inflow to each region as determined by electromagnetic cuff probes Following brief anterior descending artery occlusion (120 sec), a characteristic rapid decline in contractile force and evolution of TQ ST segment changes was observed in the ischemic area In contrast, in the distant area increases in contractile force ($p < 0.001$) and coronary blood flow ($p < 0.002$) occurred These distant responses were essentially obliterated following transection and cannulation of the artery supplying this region ($p < 0.05$) The findings are consistent with a reflex neurovascular mechanism operating within the intact heart This reflex is rapidly activated in order to maintain adequate levels of cardiac performance despite sudden loss of functional myocardial mass

REFERENCES

1 Tennant R and Wiggers C J The effect of coronary occlusion on myocardial contraction Am J Physiol 112 351 1935
2 Tomada H Parmley W W Fryjimnra S and Matloff J M Effects of ischemia and reoxygenation on regional myocardial performance of the dog Am J Physiol 221 1718 1971
3 Grayson J and Lapin B Observations on the mechanisms of infarction in the dog after experimental occlusion in the coronary artery Lancet 1 1284 1966
4 Sonnenblick E H and Kirk E S Effects of hypoxia and ischemia on myocardial contraction Alterations in the time course of force and ischemia dependent inhomogeneity of contractility Cardiology 56 302 1971 2
5 Prinzmetal M Ekmekci A Toyoshima H Kwoczynski J K Angina pectoris III Demonstration of the chemical origin of ST deviation in classic angina pectoris its variant form early myocardial infarction and some noncardiac conditions Am J Cardiol 3 276 1959
6 Holland R P and Brooks H Precordial and epicardial surface potentials during myocardial ischemia A theoretical and experimental analysis of the TQ and ST segments in the pig Circ Res 37 471 1975
7 Sayen J J Sheldon W F Pierce G et al Polarographic oxygen the epicardial electrocardiogram and muscle contraction in experimental acute regional ischemia of the left ventricle Circ Res 6 779 1958
8 Case R B Nasser M G and Crampton R S Biochemical aspects of early myocardial ischemia Am J Cardiol 24 766 1969
9 Schwartz A Wood J M Allen J C et al Biochemical and morphologic correlates of cardiac ischemia I Membrane systems Am J Cardiol 32 46 1973
10 Wollenberger A and Krause E Metabolic control characteristics of the acutely ischemic myocardium Am J Cardiol 22 349 1968
11 Jennings R B Sommers H M Herdson P B and Kaltenbach J P Ischemic injury of myocardium Ann N Y Acad Sci 156 61 1969
12 Wollenberger A and Shahar L Anoxia induced release of noradrenaline from isolated perfused hea.. Nature 207 88 1965
13 Gudbjarnason S Puri P S and Mathes P Biochemical changes in non infarcted heart muscle following myocardial infarction J Molec Cell Cardiol 2 [illegible] 1971
14 Brooks H L Al Sadir J Cutiletta A and Pes[illegible] L Cyclic 3 5 AMP activity in distant non ischemic myocardium during myocardial infarction Clin Res 22 266A 1974 (abst)
15 Polimeni P I and Al Sadir J Expansion of the extracellular space in the non ischemic zone of the infarcted heart and concomitant changes in tissue electrolyte contents Circ Res 37 7?5 197?
16 Kaltenback J P and Jennings R B Metabolism of ischemic cardiac muscle Circ Res 8 ?07 1960
17 Driscol T E and Eckstein R W Coronary inflow and outflow responses to coronary artery occlusion Circ Res 20 485 1967
18 Levy M N and Cutarelli, R Effect of acute coronary artery ligation upon blood flow to the normal myocardium Am J Cardiol 13 48 1964
19 Berne R M and Rubio R Factors influencing coronary resistance in the ischemic heart Circulation Suppl IV 240 1969
20 Howe B B Fehn P A and Pensinger R R Comparative anatomical studies of the coronary arteries of canine and porcine hearts Acta Anat 71 13 1968
21 Schaper W Comparative arteriography of the collateral circulation of the heart Amsterdam 9 ? North Holland Publishing Company
22 Brooks H., Al Sadir J Schwartz J Harper P and Resnekov L Biventricular dynamics during [illegible] tated anteroseptal infarction in the porcine heart Am J Cardiol 36 765 1975
23 Newman W H and Walton R P Strain gauge [illegible] recordings from an acutely ischemic area of the le[illegible] ventricle J Appl Physiol 23 398 1967
24 Holland R Pashkow F., and Brooks H Atraumatic epicardial electrode and rapid sampling switch for cardiac surface mapping J Appl Physiol 37 4?4 19?4
25 Snedecor G W and Cochran W G Statistical methods Ames Iowa 1967 Iowa State College Press pp 106-111
26 Holland R P and Brooks H The QRS complex during myocardial ischemia An experimental analysis in the porcine heart J Clin Invest 57 541 19?6
27 Aviado D M Jr and Schmidt C F Reflexes and stretch receptors in blood vessels heart and lung Physiol. Rev 35 247 1955
28 Endoh M Kimura T and Hashimoto K Effects of periarterial nerve stimulation on the contraction automaticity and blood flow of the canine ventricular myocardium Tohoku J Exp Med 106 309 19??
29 Nonidez J F Distribution of the aortic nerve fibers and the epitheloid bodies (supracardial paraganglica) in the dog Anat Rec 69 299 1937
30 Hirsch E F and Orme J F Sensory nerves of the human heart Arch Pathol 44 325 1947
31 Jarisch A and Richter H Die afferenten Bahnen des Veratrineffekts in den Herznerven Arch Exp Pathol Pharmakol 193 355 1939
32 Hanley R Raizner A Inglesby T and Skinner S J Response of the renal vascular bed to acute coronary artery occlusion Am J Cardiol 29 803 1972
33 Falicov R E Mills C J and Gabe I T The response of the renal and femoral vascular beds to coronary embolization in the dog Cardiovasc Res 9 151 19?5

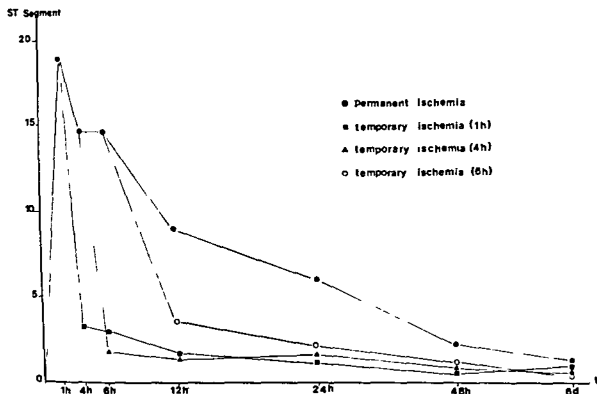


Fig 2 Evolution of the height of the ST segment in different groups of ischemia at different time interval

Histoenzymatic study was carried out on 56 hearts washed in cold saline (4° C) and frozen at −80 C in liquid nitrogen Transverse sections 5 μ thick were cut on a cryostat 1 cm from the apex Phosphorylase (Pase) and succinyl dehydrogenase (SDH) were chosen because their activity decreases after ischemia [5 14 1] Results were expressed as a percentage of the total area of the left ventricular section

Capillary injection study of colloidal carbon in 10 animals was undertaken in order to measure the area of vascular permeability Under ether anesthesia following intravenous injection of 1 per cent Procaine sulfate in order to arrest the heart in diastole the abdominal aorta was perfused with a 2 per cent solution of buffered glutaraldehyde solution for fixation followed by the injection of a 20 per cent suspension of colloidal carbon in gelatin Sections were obtained at 4° C measured 50 to 100 μ in thickness and were embedded in paraffin for permanent sections The extent of the area of infarction and the area of carbon black injection was measured by planigraphy

Results

1 ECG study

a Group I Permanent ligation (47 animals) After 1 hour of coronary occlusion the ST segment elevation was 18 ± 1 4 mm Beyond 12 hours the ischemic ST changes diminished and returned to normal toward the fifth or sixth day Q waves appeared after the first hour and became progressively larger The Q wave over QRS ratio was maximal the first day (0 62 ± 0 06) and persisted at 7 days (0 76 ± 0 06)

b Group II Temporary ligation (53 animals) When the ligature was released before 6 hours of ischemia the ST segment elevation was 2 5 ± 1 7 after 1 hour of reperfusion This difference from the control groups remained significant up to 24 hours ($p < 0\ 001$) of evolution (Fig 2) At 7 days the regression of the Q wave was significantly different from the control group ($Q = 0\ 29 \pm 0\ 07$) ($p < 0\ 001$) (Fig 3) When the ligature was released between 12 to 24 hours of ischemia there was no significant difference between the con rol and the perfused animals

2 Histologic study

The effect of coronary artery reperfusion on the extent of myocardial infarction

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Coronary artery bypass during acute myocardial infarction is based on the principle of salvaging myocardial cells in the early phase following coronary obstruction However the effects of early coronary artery reperfusion on infarct size remain controversial The present study was undertaken in an effort to determine the conditions under which reperfusion is beneficial or detrimental



Fig 1 Technique of temporary ligation

Methods

Wistar rats weighing an average of 250 grams, were divided into two groups

Group I (control group) The left coronary artery was occluded with the technique of Johns and Olson [11] as modified by Selye et al [18] Under ether anesthesia through a left thoracotomy incision a ligature was placed around the left coronary artery The animals were killed at regular intervals 1 hour 6 hours, 12 hours 24 hours 48 hours and 7 days following coronary artery ligation

Group II (reperfusion group) The coronary artery ligature was released by traction on the exteriorized portion of the suture (Fig 1) Reperfusion was carried out 1 hour, 6 hours 12 hours and 24 hours after coronary occlusion The rats in this group were killed at 6 hours 12 hours 24 hours 48 hours and 7 days following coronary artery reperfusion

Electrocardiographic (ECG) study of 100 rats was done by recording at regular intervals during the first 24 hours and during the first week under ether anesthesia in the ventral decubitus position, using four extremity leads and one midline precordial lead The paper speed was 15 mm per second, voltage was standardized to give a deviation of 1 cm The leads used were D_1, aV_L and the midline precordial

Histologic study was performed on 121 hearts treated by immediate fixation of a 15 per cent solution of buffered formalin Transverse sections were obtained 1 cm from the apex and stained with hematoxylin and eosin safran, and Masson's trichrome stains The portion of damaged myocardium was measured and expressed as a percentage of the total area of the ventricular section

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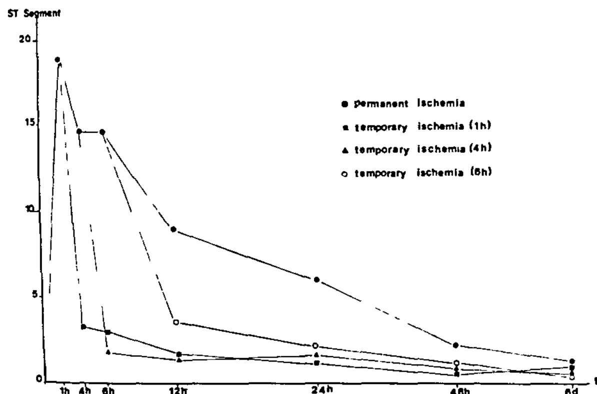


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2 Histologic study

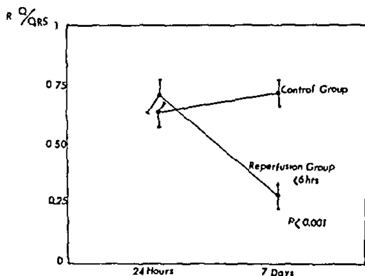


Fig 3 Evolution of the Q wave over QRS ratio The difference between the control group and the reperfusion group (before 6 hours) is significant at 7 days ($p < 0\,001$)

a Group I Permanent ligation (40 rats) At 48 hours the size of the infarction was 60 ± 15 per cent of the cross sectional area of the left ventricle at 1 cm from the apex The infarction involved the anterolateral wall and a portion of the posterior wall of the left ventricle No thrombosis of the coronary artery occurred at the site of the ligature

b Group II Temporary ligation (81 animals) When the ligature was released before 6 hours the mean extent of the infarction was 41 ± 12 per cent of the cross sectional area at 48 hours of reperfusion The difference from the control group was significant ($p < 0\,001$) (Fig 4) When the ligature was released after 12 to 24 hours of ischemia, the mean extent of the infarction was 66 ± 14 per cent, which is not significantly different from the control group There was a diffuse hemorrhagic infiltration of the necrotic myocardial tissue (Fig 5)

3 Histoenzymatic study

a Group I Permanent ligation (14 animals) The normally intense phosphorylase activity of the myocardium completely disappeared from the ischemic area within the first 2 hours The border between normal and ischemic myocardium was sharply defined without a transitional zone The tetrazolium in nitroblue stain revealed succinyl dehydrogenase in the form of formazan deposits which appeared as fibrils (form F) at each extremity of the nucleus and along the length of the myofibrils The extent of this zone was 64 5 ± 2 8 per cent of the total cross sectional area of the left ventricle at 1 cm from the apex After 6 hours of ischemia comparison betwee phosphorylase and succinyl dehydrogenase acti ity was such that two different zones could be defined a central zone of necrosis in which myocardial cells were dissociated retracted and occupied by dense clumps of formazan and a marginal zone of ischemia involving 20 to 30 per cent of the surface area, which was characterized by a lack of phosphorylase activity and abnormal succinyl dehydrogenase activity represented by granules of formazan measuring 1 to 3 μ (Fig 6 and 7) After 12 to 48 hours of ischemia, the necrotic area lost all staining properties and extended into the marginal zone

b Group II Temporary ligation (37 animals) When the ligature was released before 6 hours following 12 hours of reperfusion the mean extent of the negative phosphorylase area was 45 7 ± 5 4 per cent The difference was significant as compared to the control group At 6 hours of reperfusion the granular activity of SDH was reduced to a few scattered foci by the extension of the normal SDH activity of the myocardium After a 7 days of reperfusion the difference with the control group was even more obvious When the ligature was released after 12 or 24 hours of ischemia following 12 hours of reperfusion the phosphorylase activity was not significantly different from that of the control group (Figs 8 to 10)

4 Capillary injection study

a Group I Permanent ligation (8 animals) In all specimens the area of no reperfusion was 65 ± 2 5 per cent of the cross sectional area of the left ventricle which was similar to the phosphorylase negative zone

b Group II Temporary ligation (62 animals)

Ligation 15 to 30 minutes The carbon positive areas varied with the length of time o reperfusion Immediately following release of th ligature it was 34 per cent of the ischemic zon (phosphorylase negative zone) After 30 minutes it was 60 per cent After 1 to 6 hours of reperfu sion only 30 per cent of the ischemic zone wa injected After 24 hours and more of reperfusion 60 per cent of the ischemic area was injecte (Figs 11 to 13)

Ligation 2 hours The curve of the reperfu sion phenomenon (Fig 13) displayed a configura tion which resembled that of the preceding grou but with a wider extension of the area of reperfu sion

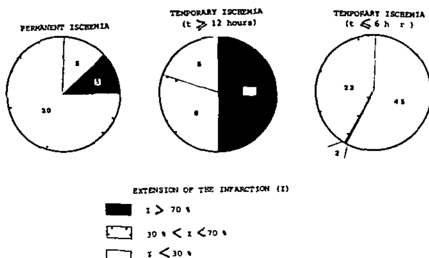


Fig 4 Diagrammatic representation of the extent of infarction after permanent ischemia and temporary ischemia The area of the infarction is expressed as a percentage of the total cross sectional area of the left ventricular section. The more severe lesions are found in the group of transitory ligation of more than 12 hours duration



Fig 5 Myocardial infarction following 24 hours of ligation (histologic examination at 48 hours) The characteristic finding is that of a diffuse and severe hemmorrhagic reaction with necrotic myocardial cells (×450)

Discussion

Much work has been done on the effects of myocardial reperfusion Due to the difficulty of model selection however most studies have restricted themselves to short initial periods of reperfusion The use of rats in this experiment allowed a large series with varying lengths of time of reperfusion

In addition the possibility of working with an entire cross section of the heart on one microscopic slide permitted precise planimetric measurement

The ECG findings showed a significant improvement in the reperfused group A clear relationship existed between the duration of the ischemia and the rapidity of regression of the ST segment elevations Return of ST segment elevations to normal can be explained by either a



Fig 6 Myocardial infarction following permanent ischemia (examination at 6 hours) (×14) *A* Phosphorylase activity absence of enzymatic activity is noted in the ischemic area *B* Succinodehydrogenase activity normal activity is seen in the nonischemic area (above) absence of activity is noted in the ischemic area (below) reduced activity in the marginal zone (ZM)

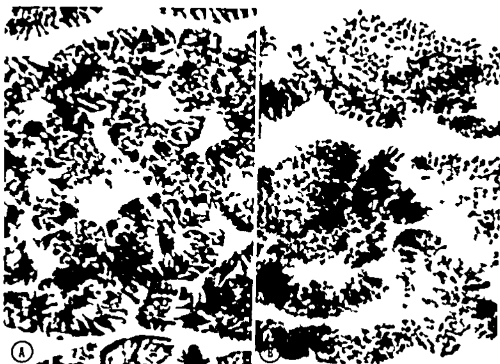


Fig 7 Infarction following permanent ischemia (examination at 6 hours) study of succinodehydrogenase activity (×1 500) *A* Normal activity in the nonischemic zone *B* Type G granules in the marginal zone

return to normal of the ischemic cells or a more rapid evolution toward necrosis However we found that in spite of the temporary appearance of a Q wave, the Q wave was significantly smaller a week later than in the control group indicating that the final extent of necrosis was decreased

These data were in accordance with the result obtained in other animals by different authors Maroko et al showed that reperfusion after 3 hours of coronary occlusion reduced ST segment elevation improved the contractility of the ischemic zone and resulted in less necrosis after

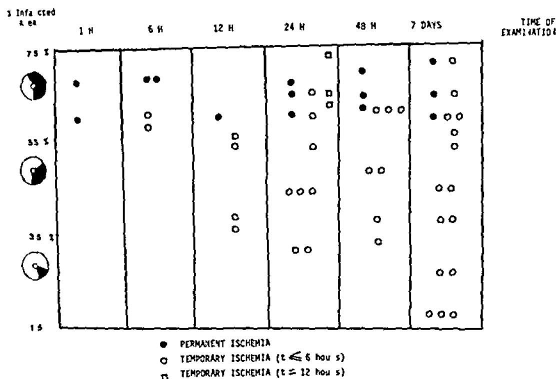


Fig 8 Diagrammatic representation of phosphorylase activity following permanent ligation less than 6 hours ligation and 12 hours ligation

24 hours as reflected by histologic appearance and myocardial CPK activity Ginks et al carried these studies further and showed that when the animal was killed 1 week after coronary reperfusion the extent of the infarction was significantly smaller than that expected by the areas of ST segment elevation before reperfusion

The results of myocardial reperfusion remain controversial Several authors have claimed that the effects are beneficial while others demonstrate increased necrosis accompanied by massive hemorrhage

These discrepancies may be the result either of different durations of occlusion before reperfusion or of different time intervals between reperfusion and examination of the heart In the present study the effects of various times of reperfusion were examined systematically Animals were killed in order to determine when reperfusion was beneficial or harmful Based on both histologic and histoenzymatic staining techniques we showed that reperfusion after 1 to 6 hours following coronary occlusion is beneficial reducing significantly the areas of infarction if the reperfusion time is at least of 12 hours duration The benefits were more obvious after 7 days



Fig 9 Myocardial infarction following temporary ischemia Limited myocardial infarction (*intramural type*) following 1 hour of ischemia examined at 12 hours (*succinodehydrogenase* activity) (×60)

Using histochemical techniques it was possible to demonstrate that the decrease in the area of the necrosis was mainly at the expense of the granular area of the SDH which corresponds to the marginal zone and therefore the salvageable zone When ischemia lasted more than 12 hours the effects of reperfusion were an extensive necrotic hemorrhage infarction This could be due to increased capillary permeability It is impor



Fig 10 Limited myocardial infarction (transmural type) following 4 hours of ischemia examined at 7 days (histologic study) (×12 5)



Fig 11 Capillary injection permanent ligation The noninjected zone corresponds to the ischemic area (×11)

tant to note that reduction of myocardial infarction size after reperfusion affected only 60 per cent of the cases The remaining 40 per cent showed no difference with the control groups This discrepancy may be the result of variation in capillary bed reperfusion as shown by colloidal carbon injection of the capillary bed after reperfusion This so called no reflow phenomenon[2 14] has been described in the reperfusion of brain[1] and kidney[20] Our study showed that the no reflow phenomenon varied in relation to the length of time of ischemia and in relation to the length of tissue reperfusion

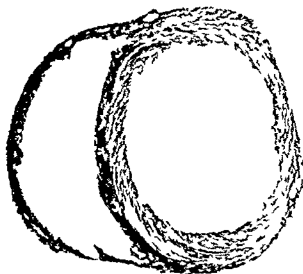


Fig 12 Temporary ligation (30 minutes ligation with a reperfusion of 30 minutes) Defect of reperfusion in the ischemic area (×11)

The no reflow phenomenon was mainly the result of myocardial edema as demonstrated by electron microscopic studies, a cause which has already been recognized by others[8 12]

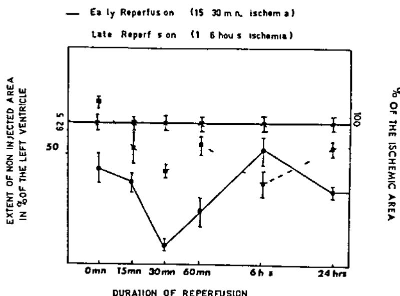
Extrapolation to patients is always hazardous not only because species differences vary but also because coronary patients have a vascular network of the myocardium which is modified by the chronicity of the disease process However this study suggests that early reperfusion may be beneficial whereas late reperfusion not only is useless but may be harmful

Summary

The effect of the reperfusion on myocardial infarction has been studied in the rat in order to assess the possible reversibility of myocardial damage

The present study deals with reperfusion of experimental myocardial infarction in the rat Two groups of animals were compared one was subjected to permanent ischemia and the other was subjected to ischemia of variable duration (1 hour to 24 hours) The differences between infarction caused by permanent ischemia and the evolution of infarction following reperfusion were studied by means of histologic (121 specimens) histoenzymatic (56 specimens) ECG (100 specimens), techniques and study of the microcirculation (70 specimens)

The size of the infarctions caused by temporary



Fg 13 Noninjected area in percentage of the cross section of the left ventricle (on the left) and of the ischemic area (on the right) in function of duration of ischemia and reperfusion The 6? per cent line represents the noninjected area after permanent ligation Colloidal carbon injection of the capillaries after early reperfusion (circles) and late reperfusion (squares) as compared with injection in nonreperfused heart (crosses) The noninjected area is presented as a percentage of the whole left ventricle (left scale) and of the ischemic area (right scale)

ischemia was found to be significantly smaller in 60 per cent of the cases as compared to the infarctions caused by permanent ischemia

Histoenzymatic study (phosphorylase activity and succinodehydrogenase activity) confirmed the existence of a marginal zone extending over one third of the surface of the ischemic myocardium reperfusion permitted the salvage of this zone and thereby diminished the extent of necrosis

The latter findings were further confirmed by the ECG study showing earlier regression of ischemic ST changes following early reperfusion

Microcirculatory changes secondary to anoxia may account for the fact that in a certain percentage of the cases early reperfusion does not prevent extension of infarction

REFERENCES

1 Ames A Wright R W Kowanda M Thurston J M and Majno G Cerebral ischemia II The no reflow phenomenon Am J Pathol **52** 437 1968

2 Bathirzade M F Kirsch, U and Hauschild U Capillareinengung bei anoxisch und ischamisch bedingtem Ausstieg des Coronawederstandes in Meerschweinchen lurzen, Virchows Arch. A 3o1 193 1970

3 Blumgart H L Gilligan D R and Schlesinger M J Experimental studies on the effect of temporary occlusion of coronary arteries II The production of myocardial infarction Am Heart J **22** 374 1941

4 Breshnahan G F Roberts R Shell W E Ross J and Sobel B E Deleterious effects of reperfusion in evolving myocardial infarction Am J Cardiol **32** 82 1974

5 Cox J L McLaughlin V W Flowers N C and Horan L G The ischemic zone surrounding acute myocardial infarction Its morphology as detected by dehydrogenase staining Am Heart J **76** 650 1968

6 Deloche A Fontaliran F Fabiani J N Pennecot G Carpentier A and Dubost Ch Etude experimentale de la revascularisation chirurgicale precoce de l infarctus du myocarde Ann Chir Thorac Cardiovasc **11** 89 1972.

7 Ginks W R Sybers H D Maroko P R Covell J W Sobel B E and Ross J Coronary artery reperfusion II Reduction of myocardial infarct size at 1 week after the coronary occlusion J Clin Invest **51** 2717 197

8 Hauschild U Bathirzade M F and Kirsch U Capillarkompression als Ischamiefolge Elektroenoptische Untersuchungen an Papillarmuskeln des Menuschen und des Meerschwienchens Virchows Arch Pathol Anat **351** 205 1970

9 Hiemeyer V Pasche H and Biehl K Influence d anticoagulants et de streptokinase sur l evolution de l infarctus de myocarde Klin Wochenschr **47** 371 1969

10 Jennings R B Effects of a transient period of ischemia on myocardial cells Am J Pathol **74** 381 1974

11 Johns T N P and Olson B I Experimental myocardial infarction I Method of coronary occlusion in small animals Am J Surg 140 675 1954

12 Kloner R A Ganote C E and Jennings R B The no reflow phenomenon after temporary coronary occlusion in the dog Circulation 54 1496 1974

13 Krug A The extent of ischemic damages in the myocardium of the cat after permanent and temporary coronary occlusion J Thorac Cardiovasc Surg 60 242 1970

14 Krug A and Korb G Durchblutungsstorungen und histologische sowie enzymhistochemische fruhverande rungen am katzerhegen nach temporarer unterbindung von koronargefassen Beitr Pathol Anat 134 29 1966

15 Krug A Blood supply of the myocardium after temporary coronary occlusion Circ Res 19 57 1966

16 Maroko P R Kjekshus J K Sobel B E Watanabe T Covell J W Ross J and Braunwald E Factors influencing infarct size following experimental coronary artery occlusions Circulation 43 67 1971

17 Maroko P R Libby P Ginks W R Bloor C M Shell W E Sobel B E and Ross J Coronary artery reperfusion I Early effects on local myocardial f[illegible] and the extent of myocardial necrosis J Clin Inv 51 2710 1972

18 Selye H Bajusz E Graslo S and Mendell P S[illegible] techniques for the surgical occlusion of coronary vess in the rats Angiology 11 398 1960

19 Sommers H M and Jennings R B Experimental acute myocardial infarction Histologic and histochemical studies of early myocardial infarcts induced by temporary or permanent occlusion of a coronary artery Lab Invest 13 1491 1964

20 Summers W K and Jamison R L The no reflow phenomenon in renal ischemia Lab Invest 25 6 1971

Comparative effects of overdrive on sinus and subsidiary pacemaker function

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Recent electrophysiological studies have accumulated significant data concerning the behavior of the normal and diseased sinus node in response to premature atrial systoles and atrial overdrive pacing [10] Specifically the duration of sinus node recovery time after rapid atrial pacing has been used as a means of diagnosing the clinical entity called the sick sinus syndrome [5] In contrast little literature is available on the effects of premature systoles and overdrive pacing on lower pacemaker sites within the A V junctional tissue and the distal conduction system [2]

The purpose of the present study is to investigate the potential differential effects of overdrive pacing on the recovery time of the sinus pacemaker and subsidiary escape pacemakers

Methods

Patient studies All patients were studied in the preprandial state after admission and observation in the coronary observation unit All studies were conducted in the cardiac catheterization laboratory A No 6 Fr four polar catheter was passed through an antecubital vein into the high right atrium and a No 6 Fr tripolar catheter was passed through the right femoral vein into the right ventricle at the level of the bundle of His Surface electrocardiogram (ECG) intra atrial bundle of His and intraventricular electrical activity were then recorded on a photographic oscillographic recorder at a paper speed of 100 mm per second Atrial pacing at 90 110 130 150 and 170 beats per minute was carried out for 30 second periods and then abruptly terminated Sinus node recovery time was measured as the time elapsing from the last pacemaker spike to the appearance of the next atrial depolarization on the intra atrial electrogram P wave configuration on the surface ECG was used to ascertain that the first escape beat terminating the pause was indeed sinoatrial in origin Subsequently the femoral catheter was repositioned at the apex of the right ventricle and a similar pacing protocol carried out utilizing rates of 90 to 150 per minute

Patient population Seven patients ranging in age from 7 to 81 years with chronic advanced A V block were studied Two patients had congenital heart block one patient had heart block secondary to aortic valve disease and four patients had idiopathic heart block No patient was taking antiarrhythmic drugs or other medication known to interfere with sinus node or subsidiary escape pacemaker function Two patients had ECG evidence of old myocardial infarction and two patients had clinical evidence for left ventricular dysfunction No patient had a febrile illness thyroid disease hypovolemia symptomatic anemia pulmonary disease arterial hypoxia acid base disturbances or electrolyte imbalances

Dog studies Five healthy mongrel dogs (15 to 20 kilograms) were premedicated with morphine sulfate 2 mg per kilogram given as an intramuscular injection After tracheal intubation the dogs were put on assisted ventilation and general

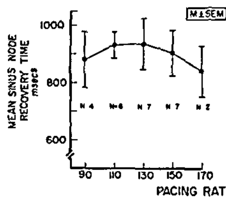
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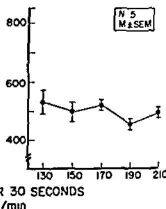
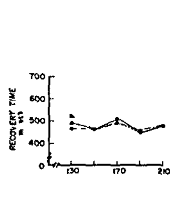


Fig 1 (*A*) The relationship between sinus node recovery time and the rate of atrial overdrive pacing in man The mean sinus recovery time remains essentially constant over a wide range of pacing rates (*B*) The relationship between sinus node recovery time and rate of atrial overdrive pacing in dogs The mean sinus node recovery time remains essentially constant over a wide range of pacing rates



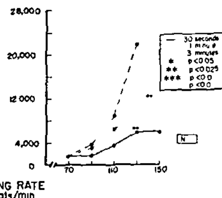
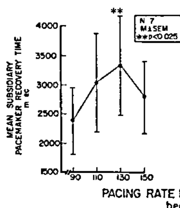


Fig 2 (*A*) The influence of duration of atrial overdrive pacing on the relationship between the sinus node recovery time and the rate of atrial overdrive pacing in dogs The sinus node recovery time is independent of the duration of overdrive at all pacing rates (*B*) The influence of duration of ventricular pacing on the relationship between the subsidiary pacemaker recovery time and the rate of ventricular pacing in dogs At all pacing durations statistically significant differences ( ) in subsidiary pacemaker recovery time are seen at rates of 110 per minute or greater when compared to those observed at an overdrive rate of 70 per minute The duration of ventricular overdrive is a significant factor (Δ) only at pacing rates of 130 and 150 per minute 3 minutes of overdrive as compared to 30 seconds of overdrive (Δ)

anesthesia was induced by sodium pentobarbital 5 mg per kilogram followed by urethane as a 20 per cent solution both given as an intravenous bolus A right thoracotomy was then performed care being taken not to injure the vagus nerve during pericardial opening and 0 1 ml of 40 per cent formaldehyde was injected into the region of the bundle of His to produce complete A V block [6] Two No 6 Fr bipolar pacing catheters were positioned at the high right atrium via the right external jugular vein Atrial electrograms and multiple surface ECG s were recorded on a photographic oscillographic recorder* at a paper speed of 100 mm per second Atrial pacing was then carried out at 130 150, 170 190 and 210 beats per minute for 30, 60 and 180 seconds at which times overdrive pacing was abruptly terminated Sinus node recovery time was taken as the time elapsing from the last pacemaker spike to the appearance of the next atrial depolarization on the intra atrial electrogram P wave configuration on the surface ECG was used to ascertain that the first escape beat terminating the pause was indeed sinoatrial in origin The pacing catheter was then advanced into the apex of the right ventricle and ventricular pacing at 90 110 130 and 150 beats per minute was carried out for 30

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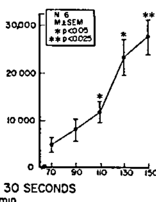


Fig 3 (*A*) The relationship between subsidiary pacemaker recovery time and the rate of ventricular overdrive pacing in man The mean subsidiary pacemaker recovery time increases up to a pacing rate of 150 per minute when a decrease is then observed The recovery time at 130 per minute is statistically significantly longer than at 90 per minute (*B*) The relationship between subsidiary pacemaker recovery time and the rate of ventricular overdrive pacing in dogs The mean subsidiary pacemaker recovery time increases linearly as rate of ventricular pacing increases The values obtained at 110 130 and 150 per minute are statistically significantly different from the escape time at 70 per minute

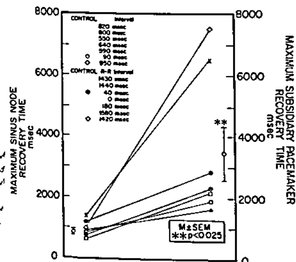


Fig 4 Comparison of the magnitude of maximum sinus node and subsidiary pacemaker recovery times in man The maximum subsidiary pacemaker recovery time after ventricular overdrive pacing exceeds the maximum sinus node recovery time in all patients. The mean maximum subsidiary pacemaker recovery time is significantly greater than the mean maximum sinus node recovery time

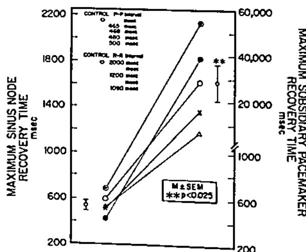


Fig 5 Comparison of the magnitude of maximum sinus node and subsidiary pacemaker recovery times in dogs The maximum subsidiary pacemaker recovery time after ventricular overdrive pacing exceeds the maximum sinus node recovery time in all dogs. The mean maximum subsidiary pacemaker recovery time is significantly greater than the mean maximum sinus node recovery time

60 and 180 seconds at each pacing rate at which times overdrive pacing was abruptly terminated

Results

ECG data In the seven patients the control P P intervals ranged from 550 to 820 msec and the control R R intervals ranged from 1140 to 1580 msec All patients except one (Patient O QRS 130 msec RBBB) had QRS durations of less than 100 msec and a His bundle spike preceded the QRS in all patients

In the five dogs the control P P intervals ranged from 469 to 500 msec and post block control R R intervals ranged from 1 091 to 2 000

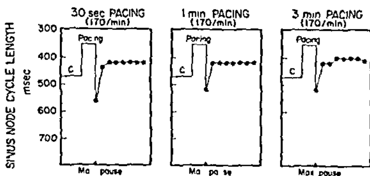


Fig 6 Return cycle lengths in one dog after 30 seconds 1 minute and 3 minutes of atrial overdrive pacing at a rate of 170 per minute Postrecovery sinus node acceleration is observed at all pacing durations

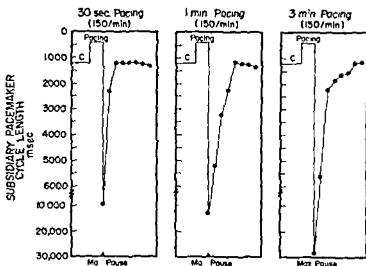


Fig 7 Return cycle lengths in one dog after 30 seconds 1 minute and 3 minutes of ventricular pacing at a rate of 150 per minute Postrecovery subsidiary pacemaker depression is observed at all pacing durations

msec Pre block QRS durations ranged from 45 to 61 msec which, following heart block ranged from 70 to 138 msec

Sinus node recovery time as a function of atrial pacing rate Six of seven patients had a normal sinus node recovery time (i e < 1 400 msecs), one patient s recovery time was minimally prolonged (Patient X, 1 400 msec) No statistically significant relationship existed between the mean recovery time of the sinus node and the rate of atrial pacing in either human subjects or experimental animals (Fig 1) In dogs, no statistically significant relationship existed between the mean recovery time of the sinus node and the duration of atrial pacing regardless of pacing rate (Fig 2 *A*)

Subsidiary pacemaker recovery time as function of ventricular pacing rate In the seven patients subsidiary pacemaker recovery time following ventricular overdrive was biphasic with the maximum mean subsidiary pacemaker recovery time observed at a ventricular pacing rate of 130 (Fig 3 *A*) In the dogs a linear relationship existed between the ventricular overdrive pacing rate and the subsidiary pacemaker recovery time with the maximum escape time observed at a pacing rate of 150 per minute (Fig 3 *B*) The linear relationship was observed regardless of the duration (Fig 2 *B*) In four dogs the nature of the relationship between the duration of overdrive and the overdrive rate with respect to subsidiary pacemaker recovery time was evaluated Statistically significant differences dependent on the rate of overdrive were seen only at rates of 110 per minute or greater at all pacing durations (Fig 2, *B*) In addition, increasing the duration of overdrive pacing produced statistically significant increases in recovery times at rates of 130 per minute or greater (Fig 2 *B*)

Sinus node recovery time vs subsidiary pacemaker recovery time In all dogs and in all human subjects maximum subsidiary escape pacemaker recovery times statistically significantly exceeded maximum sinus node recovery times (Figs 4 and 5) Maximum sinus node recovery times in human subjects ranged from 800 to 1 400 msec whereas maximum subsidiary pacemaker recovery times ranged from 1 670 to 7 600 msec Maximum sinus node recovery times in the dogs ranged from 510 to 660 msec whereas maximum subsidiary pacemaker recovery times ranged from 5 600 to 53 900 msec In man when recovery times were evaluated at similar pacing rates statistically different effects were consistently observed between sinus node and subsidiary pacemaker recovery times (Table I) In dogs when recovery times were evaluated at similar pacing durations statistically different effects were again consistently observed between sinus node and subsidiary pacemaker recovery times (Table II)

Postrecovery effects In all studies particular attention was directed at the events distant to the immediate return cycle The phenomenon of postrecovery sinus node acceleration was a consistent finding after atrial overdrive pacing (Fig 6) In contrast postrecovery subsidiary pacemaker depression was a consistent finding after ventricular overdrive pacing (Fig 7)

Discussion

Over the past 70 years isolated reports of depression of both sinus and idioventricular pacemakers by premature systoles have appeared[17]. Further observations that the degree of inhibition of spontaneous impulse formation increases in degree as the extrasystole becomes more premature and that a run of premature impulses is followed by greater inhibition than isolated premature impulses have also been reported[16,18]. Recent studies have increased our knowledge of the electrophysiological events that underlie real and apparent alterations of cardiac pacemaker function following premature systoles overdrive pacing [1, 2, 25]

That a disparity between various pacemakers with response to overdrive should exist was suggested by Vassalle s report of Purkinje fiber recovery times which were 20 times longer than spontaneous Purkinje fiber cycle lengths In contrast maximum normal sinus node recovery time has been shown to be less than two times longer than spontaneous sinus node cycle lengths[12] Lange found in dogs that when after crushing the sinus node and an A V junctional escape pacemaker predominated atrial pacing resulted in greater A V junctional recovery time than previously determined sinus node recovery time In the same study Lange also demonstrated the influence that the site of pacing had on pacemaker recovery time Specifically prolongation of A V junctional recovery time was greater after atrial pacing than after ventricular pacing Ventricular overdrive pacing however still ...d in greater depression of A V junctional than atrial overdrive had depressed sinus node In contrast to Vassalle s findings ... demonstrated little depression of idioventricular pacemakers by ventricular pacing

The underlying pathophysiological mechanisms responsible for the phenomenon of prolongation of pacemaker recovery time after overdrive pacing have been speculated upon in previous studies. Recordings of transmembrane potentials have shown that the temporary suppression of spontaneous activity in Purkinje fibers following overdrive pacing is due to a reduced slope of diastolic depolarization In addition elevations of the threshold potential prolongation of the duration of the action potential and diastolic hyperpolarization have been observed in association with overdrive suppression of cardiac pacemakers[21] It has been suggested that these electrophysiological alterations are accounted for by an accumulation of extracellular potassium and/or by the activation of an electrogenic sodium pump[1] Further it has been suggested that these latter events occur with rapid overdrive pacing in part due to the discharge of catecholamines and acetylcholine from nerve endings and tissue stores into the extracellular environment[7]

It is reasonable to assume that the difference in magnitude of suppression of sinus node and subsidiary escape pacemaker recovery times is the result of either (1) differences in underlying electrophysiological alterations resulting from overdrive pacing (2) differences in the mechanism by which the same alterations are induced (3) differences in the sensitivity of different pacemaker cells to changes in the extracellular environment or (4) differences in intrinsic pacemaker electrophysiologic mechanism For example suppression

Table I Sinus node recovery time (SNRT) vs subsidiary pacemaker recovery time (SPRT) at the same atrial and ventricular pacing rates in human subjects

No of pts	*Pacing rate (b p m)*	*Mean (msec) SNRT (±S E M)*	*Mean SPRT (±S E M)*
4	90	880 (± 99 3)	2 490 (±584 0)
6	110	928 (±10_3)	3 044 3 (±874 9)†
7	1_0	935 7 (±86 1)	3,361 4 (±864 9)‡
7	150	904 3 (±80 1)	2 800 (±617.8)§

$p < 0.05$
†$p < 0.0_$
‡$p < 0.01_5$
§$p < 0.01$

Table II Sinus node recovery time (SNRT) vs subsidiary pacemaker recovery time (SPRT) at the same durations of atrial and ventricular pacing at 150 b p m in three dogs

Duration (sec) of pacing	*Mean (msec) SNRT (±S E M)*	*Mean (msec) SPRT (±S E M)*
30	483 3 (±55 5)	6 366 (±200 3)
60	493 3 (±54 9)	10 533 (±1,598)†
180	473 3 (±35 ?)	2_ 666 (±8 596)

$p < 0.0_$
†$p < 0.0125$

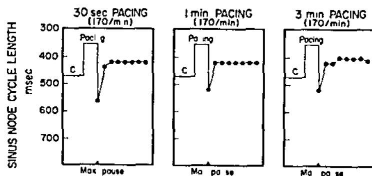


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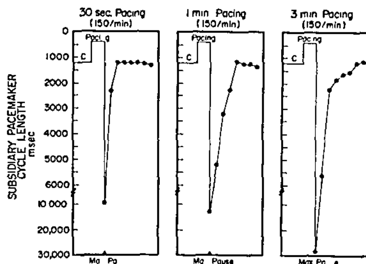


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ferent electrophysiological alterations result om overdrive pacing in more distal pacemakers) the cells of more distal pacemakers are more nsitive to changes in the extracellular environ ent or (5) species differences alone account for e difference in subsidiary pacemaker recovery nes

inical significance

Regardless of the mechanisms responsible for e differences in magnitude of recovery times of e sinus node and subsidiary pacemakers the inical importance of such a difference was ggested by observations of early investigators ohn and Lewis[2] reported clinical examples of depression of an idioventricular rhythm by single and multiple premature ectopic beats eading to Stokes Adams attacks Parkinson and ssociates and Pick and associates suggested hat instances of Stokes Adams attacks may be lue to ventricular standstill following paroxysms of atrial or ventricular tachycardia in cases of A V block Using the technique of ventricular overdrive in the setting of A V block the present study confirms and reemphasizes the possibility of Stokes Adams attacks and even death resulting from suppression of subsidiary pacemakers after ventricular tachycardia in patients with A V block

Summary

Recent evidence has suggested a difference in response to overdrive pacing dependent on the location of the pacemaker within the A V conduction system To test this hypothesis the effects of overdrive pacing were evaluated in five anesthetized dogs with experimentally induced A V block and in seven patients with advanced A V block In the animals sinoatrial node recovery times were studied over wide ranges of rates (130 to 210 beats per minute) and durations (30 to 180 seconds) of atrial pacing All sinus node recovery times were <600 msec with a mean maximum pause of 0 540 ± 0 043 seconds (M ± S E M) In contrast after ventricular pacing (rates 90 to 150 beats per minute durations 30 to 180 seconds) subsidiary pacemaker recovery times were significantly greater ($p < 0.025$) with a mean maximum recovery time of 28 4 ± 8 3 seconds In the seven patients studied all sinus node recovery times were <1 400 msecs with a mean maximum pause of 0 934 ± 0 051 seconds As seen with the experimental animals a significantly longer ($p < 0.025$) mean maximum subsidiary pacemaker recovery time of 3 55 ± 0 92 seconds was observed

The present studies in both experimental animals and in man without evidence of sinus node dysfunction showed that sinus node recovery time was independent of both rate and duration of atrial overdrive pacing In contrast subsidiary pacemaker recovery time was correlated with both rate and duration of ventricular overdrive pacing In both experimental protocols subsidiary pacemaker recovery time was shown to exceed sinus node recovery time at all rates and at all durations of pacing

Postrecovery sinus node acceleration was consistently observed after atrial overdrive pacing In contrast postrecovery subsidiary pacemaker depression characterized ventricular overdrive pacing

It is concluded that subsidiary pacemakers are significantly more susceptible to overdrive suppression than the sinoatrial node a feature of substantial clinical significance

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REFERENCES

1 Lu H H Lange G and Brookes C McC Factors controlling pacemaker action in cells of the sino atrial node Circ Res. 17 460 1965
2. Klein H O., Singer D H and Hoffman B F Effect of premature atrial systoles on rhythmicity of sino atrial node Circulation 34 III 145 1966
3 Bonke F I M Bouman L N and Van Rijn H E Change of cardiac rhythm in the rabbit after an atrial premature beat Circ Res. 24 533 1969
4 Bonke F I M., Bouman L. N and Schopman F J G Effect of an early atrial premature beat on activity of the sino-atrial and atrial rhythm in the rabbit Circ Res 24 704 1971
5 Mandel W J Hayakawa H., Danzig R and Marcus H S Evaluation of sino-atrial node function in man by overdrive suppression Circulation 44 59 1971
6 Strauss H C and Bigger J T Electrophysiological properties of the rabbit sinoatrial perinodal fibers Circ Res 31 491 1972
7 Strauss H C Saroff A L Bigger J T., and Girardina E G V Premature atrial stimulation as a key to the understanding of sino-atrial conduction in man Circulation 47 86 1973
8 Miller H C and Strauss H C Measurement of sino atrial conduction by premature atrial stimulation in the rabbit Circ. Res. 35 935 1974
9 Reiffel, J A., Bigger J T and Konstam M P The relationship between sino-atrial conduction time and sinus cycle length during spontaneous sinus arrhythmia in adults Circulation 50 924 1974
10 Ticzon A R Strauss H C Gallagher J J and Wallace A G Sinus nodal function in the intact dog

of Purkinje fiber recovery time is augmented by increases in extracellular potassium to a greater extent than is sinus node recovery time [20] Also, the influence of acetylcholine in prolonging the duration of recovery time after overdrive pacing has been shown to be greater in the sinus node and A V junction than in Purkinje fibers, as demonstrated by the effects of atropine and neostigmine on pacemaker recovery times [0] Vassalle[25] demonstrated that activation of a sodium pump may be the primary mechanism for the suppression of Purkinje fiber automaticity at pacing durations of longer than 1 minute That a similar mechanism may apply to junctional pace makers but is absent in the sinus node pace maker, is suggested by the finding in this study that the magnitude of sinus node recovery time was independent of duration of pacing while subsidiary pacemaker recovery time increased as the duration of overdrive pacing increased

The phenomenon of postpacing acceleration of the sinus node has been previously described and was confirmed in this study [0] Observations that postpacing acceleration can be eliminated by catecholamine depletion with reserpine and by catecholamine blocking agents suggest that the release of catecholamines by atrial pacing may exert a protective influence counteracting sup pression of the sinus node In our study postpac ing acceleration of subsidiary pacemakers was absent after ventricular pacing In fact postre covery beats demonstrated continuing depression of subsidiary pacemaker automaticity suggesting that fewer catecholamines are released during ventricular pacing or that subsidiary pacemakers are less sensitive to catecholamines and thus the suppression of subsidiary pacemakers is unop posed This may account in part for the greater magnitude of subsidiary pacemaker recovery times

While variable results have been reported concerning the relationship between sinus node recovery time and rate and duration of atrial pacing in subjects with no evidence of sinus node dysfunction, the results of the present study show no correlation between the magnitude of sinus node recovery time and rate or duration of atrial pacing In contrast, the present study does show a progressive prolongation of subsidiary pacemaker recovery time as the rate and duration of pacing increased This difference in recovery times between sinus node and subsidiary pacemakers may be due to differences in the complex intera tions of intracellular electrophysiological eve (e g , the slope of diastolic depolarization) extra cellular pharmacologic events (e g , concentra tions of acetylcholine and sympathetic amines in the extracellular environment) and events at the level of the cell membrane (e g activation of an electrogenic sodium pump) In turn, the interac tions between these dynamic events are probably modified by (1) the duration of overdrive pacing as suggested by Vassalle (2) the rate of pacing (3 the site of pacing or (4) a combination of the variable parameters of overdrive To further ou understanding of the determinants of recover time under different conditions of overdriv pacing it is proposed that coronary sinu concentrations of potassium acetylcholine ar catecholamines could be correlated with t magnitude of recovery times of the sinus node a subsidiary pacemakers after different rates a durations of atrial and ventricular pacing similar objective would be realized by study the changes in electrophysiologic behavior isolated sinus node A V junctional, and Purkinje fiber preparations at different rates and durations of pacing after the electrogenic sodium pump has been made inoperative by use of tetrodotoxin or lithium substitution Also the role of potential differences in coronary perfusion with atrial versus ventricular pacing is yet another variable that could be investigated

All the patients with A V block in our study had subsidiary escape pacemakers located in the area of the A V junction The sites of subsidiary escape pacemakers in the dogs were not deter mined by His bundle recordings, however the durations of the QRS complexes suggest that the postblock subsidiary escape pacemakers were located more distally in the conduction system Subsidiary pacemaker recovery time in the patients after ventricular pacing was as long as 7 6 seconds whereas subsidiary pacemaker recov ery time in the dogs after ventricular pacing was as long as 53 9 seconds While differences in duration of overdrive pacing may alone account for the observed difference in magnitude of subsidiary pacemaker recovery times in man and in dogs other explanations that must be consid ered include (1) more distal pacemakers have different intrinsic electrophysiologic properties (2) different mechanisms govern the electrophy siological events in more distal pacemakers (3)

,lediastinal teratoma masquerading as ¯liopathic enlargement of the right atrium

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Mediastinal tumors frequently mimic cardiovascular diseases and their presence must be included in the differential diagnosis of any unusual cardiac silhouette We have previously reported mediastinal tumors presenting as valvular pulmonic stenosis and congenital partial absence of the left pericardium This report concerns a patient who presented with abnormal prominence of the right heart border on routine chest roentgenography which was similar to the findings in patients with idiopathic enlargement of the right atrium[3] Exploration of the right chest after cardiac catheterization and angiography demonstrated a large teratoma adjacent to the right heart border It is important to include teratoma and idiopathic enlargement of the right atrium in the differential diagnosis of abnormalities of the right heart border on routine chest roentgenograms

Case report

A 2? year old asymptomatic man was referred for evaluation because of an abnormal chest roentgenogram There was a Grade 2/6 systolic ejection murmur along the lower left sternal border which was felt to be innocent Chest roentgenography showed a prominent bulging of the right heart border (Figs 1A and 1B) The electrocardiogram was normal except for inverted P waves in Leads II III and aV_F with a normal PR interval

Right heart catheterization demonstrated normal pressures and oxygen saturation determinations Normal circulation time proved by hydrogen inhalation study in the pulmonary artery excluded the presence of a left to right shunt A right atrial angiogram showed compression and distortion of the right atrium by an extrinsic mass (Fig 2)

A right thoracotomy revealed a firm well delineated mass extending from the anterior superior mediastinum to the right pleural cavity and attached to the pericardium Its blood supply originated from the anterior base of the neck The tumor was excised in toto and measured 9 5 by 6 by 7 cm (Fig 3) Microscopic sections showed a malignant teratoma with seminoma embryonal and endodermal sinus components as well as thymic remnants Radiation therapy and chemotherapy were subsequently initiated

Discussion

The generally benign course of idiopathic enlargement of the right atrium has been well described[3] In contrast mediastinal teratomas can compromise cardiac performance by local extension or compression Ten per cent of the tumors are malignant Nearly all teratomas occupy the upper anterior mediastinum adjacent to gross or microscopic thymic tissue In fact mediastinal teratomas are thought to arise within the anlage of the thymus[5] In the present case the teratoma was malignant and resulted in compression and distortion of the right atrium as revealed by angiography (Fig 2)

Characteristically patients with idiopathic enlargement of the right atrium present for evaluation when they are noted to have prominent bulging of the right heart border on the chest roentgenogram The diagnosis is established when right atrial enlargement is found angiographically and known causes of right atrial enlargement are

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11 Saroff A Strauss H C Bigger J T Steiner C and Giardina E G Evaluation of sinus node function in patients with sinus bradycardia Circulation 44 II 97 1971

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15 Bigger J T and Strauss H C The evaluation of sinoatrial node function in man Mev Q 9 77 1973

16 Gaskell W A On the innervation of the heart with special reference to the heart of the tortoise J Physiol 4 43 1883

17 Erlanger J and Hirschfelder A D Further studies on the physiology of heart block in mammals Am J Physiol 15 153 1905

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19 Lewis T The mechanism and graphic registration of the heart beat ed 3 London 1925 Shaw & Sons Ltd

20 Lange G Action of driving stimuli from intrinsic and extrinsic sources on in situ cardiac pacemaker tissues Circ Res 17 449 1965

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26 Steiner C and Kovalic A T W Technique for p[illegible] tion of chronic complete heart block in dog J Appl Physiol 25 631 1968

27 West T C Falk G and Cervoni P Drug alteration of transmembrane potentials in atrial pacemaker cells J Pharmacol Exp Ther 117 24[illegible] 1956

28 Cohn A E and Lewis T Auricular fibrillation and complete heart block A description of a case of Adams-Stokes syndrome including the postmortem examination Heart 4 15 1912

29 Parkinson J Papp C and Evans W The electroca[illegible] diogram of the Stokes Adams attack Br Heart J 3 17[illegible] 1941

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Fig 3 Pedunculated teratoma excised in toto measuring 9 5 by 6 by 7 cm Note cysts in body of tumor The tumor originated in the anterior superior mediastinum and extended along the ri ht heart border with posterior projection It was attached to the pericardium Microscopic sections showed a malignant teratoma with embryonal seminoma and endodermal sinus components as well as thymic remnants

Clinical assessment without cardiac catheterization may be inadequate to distinguish between a mediastinal tumor and idiopathic enlargement of the right atrium Because of the difference in prognosis and therapy cardiac catheterization and right atrial angiography are clearly indicated in such cases

Summary

A chest roentgenogram of an asymptomatic 22 year old man revealed prominence of the right heart border characteristic of idiopathic dilatation of the right atrium On further evaluation a malignant teratoma was found The importance of including teratoma and idiopathic enlargement of the right atrium in the differential diagnosis of abnormalities of the right heart border is discussed

REFERENCES

1 Vieweg W V R Brodhead C L MacNeil D J and Folkerth T L Hodgkin s disease of the anterior mediastinum presenting as pulmonic stenosis, South Med J 69 1094 19 6
2 Francis, G S Vieweg W V R O Sullivan M J., and Morgan J R Thymoma masquerading as congenital partial absence of the left pericardium Am Heart J 89 91 1975
3 Thompson S L, Vieweg W V R., Iacovoni, V E Alpert J S and Hagan A D Idiopathic enlargement of the right atrium Report of three cases Maryland State Med J In press
4 Oberman H A and Libcke J H Malignant germinal neoplasm of the mediastinum Cancer 17 498 1964
5 Schlumberger H G Tumors of the mediastinum, in Atlas of tumor pathology Washington D C 1951 Armed Forces Institute of Pathology Sec V Fasc 18
6 Pastor B H and Forte A L Idiopathic enlargement of the right atrium Am J Cardiol 8 513 1961
7 Saigusa M Morimoto K., Koike T et al Idiopathic enlargement of the right atrium Jap Heart J 3 373 1962
8 Sumner R G Phillips, J H Jacoby W J., et al Idiopathic enlargement of the right atrium Circulation 32 985 1965
9 Sheldon W C Johnson C D and Favaloro R G Idiopathic enlargement of the right atrium Report of four cases Am J Cardiol 23 278 1969
10 Tenckhoff L Stamm S J and Beckwith, J B Sudden death in idiopathic (congenital) right atrial enlargement Post mortem findings and review of cases Circulation 40 227 1969
11 Eshaghpour E Olley P M and Collins G F N Idiopathic right atrial enlargement in childhood, Am Heart J 78 373 1969
12 Tajik, A. J Broadbent J C and Schattenberg T T Idiopathic right atrial enlargement with pericardial effusion Chest 63 450 1973



Fig 1A Posteroanterior chest roentgenogram showing prominent bulging of the right heart border due to a teratoma originating in the anterior mediastinum



Fig 1B Right anterior oblique chest roentgenogram demonstrating posterior extension of the tumor

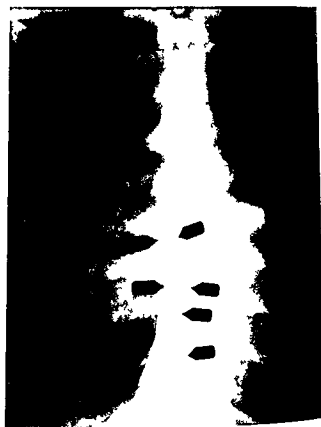


Fig 2 Compression and distortion of the right atrium (arrows) due to external compression by the teratoma originating in the anterior mediastinum Despite right atrial compression there was no pressure gradient between the inferior and superior vena cava and the right atrium

excluded[6-9] Rarely, rhythm disturbances pericardial effusion and sudden death can occur in this syndrome[10-12] The differential diagnosis of enlargement of the right heart border includes atrial septal defect, partial or total anomalous pulmonary venous return Ebstein s anomaly tricuspid valvular disease hypoplastic right ventricle pulmonic stenosis and pulmonary hypertension Moreover pericardial cyst and cardiac or pericardial tumors may distort the right heart border

Our patient was asymptomatic and had a normal physical examination findings commonly seen in patients with idiopathic enlargement of the right atrium His posteroanterior chest roentgenogram bore a striking resemblance to radiographic findings in patients with idiopathic enlargement of the right atrium[3] The right anterior oblique projection revealed that the mass extended posteriorly, thus suggesting that the distortion of the right heart border was not right atrium alone (Fig 1) However a primary right atrial tumor or a pericardial cyst can also present in this fashion Although the right atrial angiogram demonstrated compression and distortion of the right atrium no significant pressure difference existed between the inferior and superior vena cava and the right atrium It is likely that hemodynamic embarrassment would have occurred in our patient if his tumor had been allowed to expand



Fig 1 Transverse intimal tear (*B*) above aortic valve (C) and coiled intima within left subclavian artery (*A*)

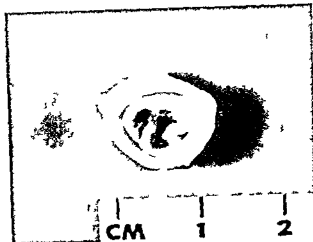


Fig 2 Cross section of left subclavian artery showing lumen occluded by torn coiled intima of aorta



Fig 3 Large false aortic channel has been opened longitudinally Note atherosclerotic change True aorta is small and circular

intimal ridge represented the entrance of this chronic dissection This dissection extended the entire length of the aorta to the iliac bifurcation The true lumen of the abdominal aorta was small and most of the aortic cross section was occupied by the endothelialized false channel (Fig 3) The false channel showed marked atherosclerotic change In contrast the true aortic intima was free of atherosclerosis The celiac and mesenteric arteries were supplied by the true aortic lumen Both renal arteries communicated with the false aortic channel Only the right renal artery was dissected These findings correlated with x ray studies that showed a poor nephrogram on the right side The re entry of the chronic dissection occurred to the right of the midline at the level of the origin of the iliac arteries

The heart weighed 495 grams The hypertrophied left ventricle showed interstitial fibrosis with no inflammation Cardiac fat was not increased A 0 2 cm tan vegetation was present along the edge of the lateral cusp of the aortic valve It was composed largely of fibrin The coronary arteries showed severe atherosclerotic disease They were not involved in the dissection A recent thrombus occluded the left circumflex coronary artery 3 cm from its origin No myocardial infarction was present Both kidneys were normal in size and weight They had granular surfaces and showed minimal cortical thinning

Microscopically acute arteritis was not present in any vessel The vascular and glomerular lesions of the kidneys were consistent with SLE They included marked intimal proliferation and perivascular edema and fibrosis with patchy infiltration by lymphocytes The glomeruli were hypercellular and lobulated No glomeruli showed fibrinoid necrosis Thickened basement membranes and fibrin thrombi were present in the capillary

Acute dissecting aneurysm of the aorta as the fatal event in systemic lupus erythematosus

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Aneurysm formation is a rare complication of systemic lupus erythematosus (SLE) A search of the literature yielded one case of coronary artery aneurysm in a 24 year old woman with SLE[1] Only one instance of an aortic aneurysm in a patient with SLE has been reported It developed during replacement of an aortic valve and was associated with marked mucoid degeneration The present report describes an extensive dissecting aneurysm of the aorta in a 34 year old man with a 22 year history of documented SLE He received corticosteroids throughout the course of his disease The autopsy findings also illustrate the adverse effects of long term steroid therapy on the cardiovascular system

Case report

The patient was admitted for evaluation of sudden severe chest pain that radiated to the right shoulder and neck accompanied by shortness of breath and loss of consciousness A diagnosis of SLE had been made at age 12 and the patient had been maintained on varying doses of corticosteroid preparations Documented hypertension with albuminuria had been present for the last 5 years Current medications included reserpine methyldopa methylprednisolone furosemide and KCl His past medical history included psoriasis and an appendectomy He had suffered multiple compression fractures of the lumbar spine secondary to chronic steroid therapy

Three years prior to this admission a gradually widening mediastinum was noted on serial chest x rays An aortic diastolic murmur was heard for the first time 9 months prior to this admission

Physical examination revealed a stuporous man in moderate distress No blood pressure was obtained in the right arm although a pulse of 80 per minute was recorded Left arm blood pressure was 110/90 mm Hg with a barely palpable pulse Right calf blood pressure measured 300/140 mm Hg His respiratory rate was 24 per minute and his temperature was 37° C Psoriatic lesions were present on the ears scalp trunk and extremities A V nicking and exudates were seen on fundoscopic examination A bruit was heard over the right carotid artery and the pulse was bounding A Grade 3 (of a maximum 4) systolic and diastolic murmur was heard at the second intercostal space in the left midclavicular line A bruit in the midepigastrium radiated to both iliac and femoral arteries Femoral pulses were palpable bilaterally The remainder of the physical examination was normal

Laboratory studies The patient had a mild normocytic anemia (hemoglobin 10 6 Gms) and proteinuria His blood urea nitrogen was 20 mg per 100 ml and creatinine was 1 3 mg per 100 ml Electrocardiograms showed left ventricular hypertrophy left bundle branch block and nodal rhythm An aortogram showed extensive dissection of an aortic aneurysm that was considered inoperable Other studies performed were within normal limits

An unsuccessful attempt was made to control his blood pressure with sodium nitroprusside and trimethaphan camsylate (Arfonad) The patient lapsed into coma and died 36 hours after admission

Pathologic findings

At autopsy 1 000 c c of free blood were found in the peritoneal cavity and hemorrhage (200 c c) was seen in the left retroperitoneum Two centimeters above the aortic valve a totally circumferential tear in the intima of the aorta was found (Fig 1) This torn intima was spiraled upon itself and coiled so as to partially occlude the left subclavian artery at its origin from the aortic arch (Fig 2) The left common carotid artery was not involved in the dissection The right innominate and right internal carotid arteries were dissected the right subclavian artery was spared In addition to this acute event, a chronic dissection of the aorta was found A saccular aneurysm measuring 3 cm in diameter was located immediately distal to the origin of the major neck vessels in the ascending aorta A rounded smooth

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disease Acquired toxoplasmosis does occur in the asymptomatic adult population Recent literature cites increasing numbers of cases of acquired toxoplasmosis in compromised hosts Included in these reports are three cases of toxoplasmosis in patients with SLE All 3 were symptomatic of the infection and each had received corticosteroids and an antimetabolic drug

The authors thank Dr Delver R Cain for reviewing the pathology

REFERENCES

1 Benisch, B M and Pervez N Coronary artery vasculitis and myocardial infarction in SLE N Y State J Med. 74 873 1974
2 Bernhard G C Lange R L and Hensley G T Aortic disease with valvular insufficiency as the principal manifestation of SLE Ann Intern Med 71 81 1969
3 Shearn M A The heart in SLE Am Heart J 58 452 1959
4 Brigden W Bywaters E G Lessof M H and Ross I P The heart in SLE Br Heart J 22 1 1960
5 Hejtmancik M R Wright J C Quint R and Jennings F L The cardiovascular manifestations of SLE Am Heart J 68 119 1964
6 Dubois E L editor Lupus erythematosus A review of the current status of discoid and systemic lupus erythematosus and their variants ed 2 Los Angeles 1974 University of Southern California Press p 404
7 Libman E and Sacks B A hitherto undescribed form of valvular and mural endocarditis Arch Intern Med. 33 701 1924
8 Gross L The heart in atypical verrucous endocarditis Libman Anniv 2 5?7 193? the International Press
9 Harvey A M Schulman L E Tumulty P A Conley C L and Schoenrich, E H SLE—a review of the literature and clinical analysis of 138 cases Medicine 33 291 1954
10 Shulman H J and Christian C L Aortic insufficiency in SLE Arthritis Rheum 12 138 1969
11 Armas Cruz R Harnecker J Ducach G., Jalil Y and Gonzalez F Clinical diagnosis of SLE Am J Med. 25 409 1958
12 Bonfiglio T A Botti R E and Hagstrom J W Coronary arteritis occlusion and myocardial infarction due to lupus erythematosus, Am Heart J 83 153 1972
13 Bulkley B H and Roberts W C The heart in SLE and the changes induced by corticosteroid therapy A study of 36 necropsy patients Am J Med 58 243 1975
14 Townsend J J Wolinsky J S Baringer J R and Johnson P C Acquired toxoplasmosis Arch Neurol 32 335 1975
15 Gleason T H and Hamlin W B Disseminated toxoplasmosis in the compromised host Arch. Intern Med 134 1059 1974

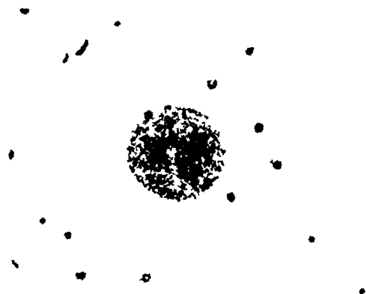


Fig 4 Pseudocyst of toxoplasma within basal ganglia area of brain (Hematoxylin and eosin ×800)

loops There was no evidence of severe renal ischemia The onion skin lesion was noted about the splenic arterioles Small perineural and periadrenal arteries were markedly thickened Patchy mucoid degeneration but no cystic change was found in the aorta In all of the dissected vessels the tear occurred at the level of the media The intima and inner two thirds of the media were central to the false channel and the outer third of the media and adventitia were peripheral to the false channel

The spleen and lymph nodes were somewhat lymphoid depleted Within a few nodes sarcoid like epithelioid granulomas could be found Some showed central necrosis No giant cells were present Acid fast and fungal stains were negative

Numerous pseudocysts of toxoplasma were found in sections of the basal ganglia and cortex of the brain (Fig 4) No free organisms were found and no pseudocysts were found in any other organs

Discussion

Cardiovascular manifestations of SLE are fairly common and have been discussed in several review articles[2-4] Our patient illustrates several of these abnormalities including an enlarged heart cardiac murmurs, hypertension and myocardial fibrosis Libman and Sacks[7] and Gross[8] reported that verrucae were most frequently found on the tricuspid valve More recent publications state that these lesions occur most often on the mitral valve[5,9] This heart showed a small vegetation on the aortic valve, the second most frequently affected valve in SLE

Systolic murmurs have been reported in two thirds of patients with acute SLE[3] These murmurs are nonspecific since they have many causes including fever, anemia and tachycardia In contrast, diastolic murmurs are infrequent in this group of patients[3,6] and are usually associated with valvular abnormalities[2,5] Valvular vegetations or thinning of the valve leaflets with perforation may cause aortic insufficiency[4] Two observers[10] found mucoid degeneration in the aortic valve suggestive of Marfan's syndrome These authors emphasize that the development of a diastolic murmur of aortic insufficiency is a poor prognostic sign in a patient with SLE The appearance of a diastolic murmur 9 months before the death of our patient may correlate with the development of the valvular vegetation but more likely marks the progressive widening of the aorta secondary to the aneurysm

The reported incidence of hypertension in patients with SLE varies from 8 per cent[11] to 44 per cent[4] In our patient as in most patients with SLE who develop hypertension, significant renal lesions were found

Coronary arteritis resulting in lumenal occlusion and myocardial infarction are rare manifestations of SLE This sequence has been described in four young women[1,12] In each case, coronary arteritis was severe and atherosclerosis was absent We believe that the severe coronary atherosclerotic changes seen in our patient may be manifestation of the adverse effects of long term corticosteroid therapy on the cardiovascular system Bulkley and Roberts[13] recently compared a group of SLE patients who received long term steroid therapy (average 38 months) with a group of pre-steroid era SLE patients They found that steroids administered for more than 1 year altered the frequency with which various cardiac lesions of SLE were found at autopsy In addition they noted the increased incidence and accelerated severity of hypertension left ventricular hypertrophy and atherosclerosis in those SLE patients who had received corticosteroids for extended periods of time No instance of aortic aneurysm was reported in their series

Of interest is the unexpected finding of numerous pseudocysts of toxoplasma within the brain The patient presented no symptoms to suggest a central nervous system disorder or disseminated

disease Acquired toxoplasmosis does occur in the asymptomatic adult population Recent literature[1-15] cites increasing numbers of cases of acquired toxoplasmosis in compromised hosts Included in these reports are three cases of toxoplasmosis in patients with SLE All 3 were symptomatic of the infection and each had received corticosteroids and an antimetabolic drug

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1. Benisch, B M and Pervez N Coronary artery vasculitis and myocardial infarction in SLE N Y State J Med 74 873 1974
2. Bernhard G C Lange R L and Hensley G T Aortic disease with valvular insufficiency as the principal manifestation of SLE Ann Intern Med 71 81 1969
3. Shearn M A The heart in SLE AM HEART J 58 452 1959
4. Brigden W Bywaters E G Lessof M H and Ross I P The heart in SLE Br Heart J 22 1 1960
5. Hejtmancik M R Wright J C Quint R and Jennings F L The cardiovascular manifestations of SLE AM HEART J 68 119 1964
6. Dubois E L editor Lupus erythematosus A review of the current status of discoid and systemic lupus erythematosus and their variants ed 2 Los Angeles 1974 University of Southern California Press p 404
7. Libman, E and Sacks B A hitherto undescribed form of valvular and mural endocarditis Arch Intern Med. 33 701 1924
8. Gross L. The heart in atypical verrucous endocarditis Libman Anniv 2 527 1932 the International Press
9. Harvey A M Schulman L E Tumulty P A Conley C L and Schoenrich E H SLE—a review of the literature and clinical analysis of 138 cases Medicine 33 291 1954
10. Shulman H J and Christian C L Aortic insufficiency in SLE Arthritis Rheum 12 138 1969
11. Armas Cruz R., Harnecker J Ducach G Jalil Y and Gonzalez F Clinical diagnosis of SLE Am J Med 25 409 1958
12. Bonfiglio T A Botti R E and Hagstrom J W Coronary arteritis occlusion and myocardial infarction due to lupus erythematosus AM HEART J 83 153 1972
13. Bulkley B H, and Roberts W C The heart in SLE and the changes induced by corticosteroid therapy A study of 36 necropsy patients Am J Med 58 243 1975
14. Townsend J J Wolinsky J S Baringer J R and Johnson P C Acquired toxoplasmosis Arch Neurol 32 335 1975
15. Gleason T H and Hamlin W B Disseminated toxoplasmosis in the compromised host Arch Intern Med 134 1059 1974

Review

Aortic stenosis, angina pectoris, and coronary artery disease

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The presence of coronary artery disease in patients with aortic stenosis was noted in many pathologic studies prior to the advent of cardiac surgery [1-10] Most authors considered the prevalence of coronary disease to be about that which would be expected on the basis of the age and sex of the patients with aortic stenosis Some felt that there was increased association,[5] however, while others believed that coronary disease was less frequent in patients with aortic stenosis than would be expected [2, 8, 9]

Relatively little attention was given to the problem of associated coronary disease during the period of development of surgical treatment for aortic stenosis in the 1950's and early 1960's [11-16] Emphasis was placed on the hemodynamic evaluation of the valvular lesion and while the association of coronary disease in some patients was recognized, it did not appear to be frequent in the patients considered for surgery who in that era were largely under 60 years of age In any event it was not amenable to systematic diagnosis or definitive surgical therapy With the advent in the 1960's of coronary arteriography, and with the increasing application of open heart surgery to patients in the older age groups,[17-22] a renewal of interest in the subject occurred The report of Linhart and associates [23] indicating that significant coronary artery disease was present in 63 per cent of a consecutive series of patients with aortic stenosis was particularly influential Other pathologic and arteriographic studies also demonstrated a frequent association [24-29] With the advent of coronary artery bypass surgery and its increasingly frequent use in combination with valve replacement surgery in the 1970's,[30-40] the diagnostic aspects of this problem assumed a new importance

The diagnosis of coronary artery disease in patients with aortic stenosis is usually considered to be very difficult, since angina pectoris and electrocardiographic (ECG) changes are produced by either condition There also remains some uncertainty about the true incidence of coronary artery disease in patients with aortic stenosis particularly in those with and without angina pectoris and those in various age groups The present study was undertaken to provide some answers to these questions

Patients studied and methods

This study deals primarily with 173 patients who represent all of the patients seen at this institution during the years 1970 to 1973 inclusive who were 40 years of age or older, had hemodynamically significant aortic valvular stenosis as an essentially isolated valvular lesion and had a technically satisfactory selective coronary arteriogram as part of their cardiologic evaluation The group includes 156 who later had surgical treatment for aortic stenosis at this institution, with or without simultaneous coronary bypass surgery The cardiac catheterization and angiographic studies were performed at this institution in 100 of these and elsewhere in 56 Also included are 17 who did not have aortic valvular surgery for various reasons even though cardiac catheterization did show hemodynamically significant aortic stenosis all but one of these a man who died suddenly the day before scheduled surgery had their angiographic studies

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Table I The number of patients with four grades of coronary artery disease in the coronary arteriogram according to age and the presence or absence of angina pectoris

Severity of coronary disease	*Age (yr)* 40 49		50 59		60 69		70 81	
	Angina	*No angina*	*Angina*	*No angina*	*Angina*	*No angina*	*Angina*	*No angina*
0	4	2	14	8	6	8	1	1
+	1	1	7	5	10	1	3	4
++	1	0	3	0	11	2	7	0
+++	3	0	15	3	25	6	17	4

in this institution Reference is also made to the 148 patients 40 years of age or older who had surgical treatment of isolated aortic valvular stenosis during 1970 to 1973 without preoperative coronary arteriography

Aortic stenosis was considered hemodynamically significant if the calculated aortic valve area was less than 0 80 cm² per square meter [2] One patient was included although the aortic valve area was 1 1 cm² per square meter because the stenosis was considered significant both clinically and at the time of operation and aortic valve replacement was carried out In four patients the cardiac output and hence the aortic valve area were not determined but in each of these the transaortic systolic pressure gradient exceeded 40 mm Hg and severe stenosis was confirmed at operation Eleven patients were included although the left ventricular pressure had not been determined in each of these the aortic stenosis was obviously severe at the time of operation and aortic valve replacement was carried out A twelfth patient who was included although the gradient and valve area were not determined had mild to moderate aortic stenosis at operation and had debridement valvotomy procedure rather than aortic valve replacement coronary arteriography was normal in this patient and his symptoms of moderate dyspnea and angina on effort were therefore attributed to moderate aortic stenosis

Patients with mixed aortic stenosis and regurgitation were included if the stenosis was considered the predominant lesion This conclusion required a demonstration of a pressure gradient of more than 50 mm Hg an arterial pulse of slow rising late peaked type and a visual evaluation at the time of operation that the stenosis was marked and was the predominant lesion Patients with functionally significant mitral valvular disease detected clinically by cardiac catheterization or at operation were not included All of the aortic valves in this series of patients showed calcification although this was not prerequisite to inclusion

Coronary artery disease was graded absent if the arteries appeared completely normal and mild if there were areas of irregularity or narrowing of less than 50 per cent of the lumen caliber or if calcification in the vessel wall was seen without luminal narrowing It was graded moderate if one or more areas of narrowing in the range of 50 to 70 per cent were present and severe if one or more areas of narrowing greater than 70 per cent were present Statistical significance was determined by the chi square method In much of the analysis the normal and mild cases and the moderate and severe cases are grouped together giving one group with no significant lesions and a second group with significant occlusive coronary artery disease Two patients were included who had selective study of only one of the two main coronary arteries showing severe lesions on the side which was visualized Patients who showed no severe lesions in incomplete studies were not included

Results

The number of patients with the four grades of coronary artery disease according to age and the presence or absence of angina pectoris is given in Table I Significant occlusive coronary lesions were found in 56 per cent of the total group including 53 per cent of the 156 surgical patients This figure may overestimate the true over all incidence because coronary arteriography was performed more frequently in patients with clinical evidence of coronary disease The lower limit

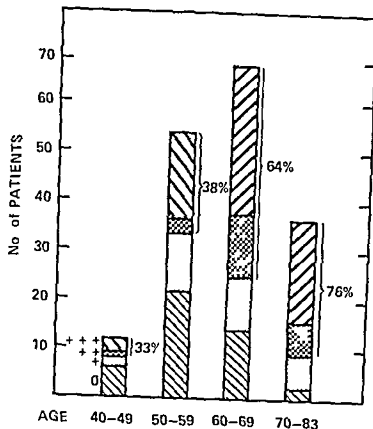


Fig 1 The incidence of coronary artery disease in 173 patients with aortic stenosis according to age Significant coronary disease (+ + or + + +) is more frequent in those aged 60 to 69 years than those aged 50 to 59 (P = < 0 01) The differences between those aged 40 to 49 and 50 to 59 and between those aged 60 to 69 and 70 to 83 are not statistically significant

of the true over all incidence may be estimated from the group of 87 surgical patients in 1973 in whom coronary arteriography was performed in 59 and significant coronary disease was found in 32, or 38 per cent of the total Thus the true over all incidence in the surgical patients is probably in the range of 40 to 50 per cent

The incidence of significant coronary disease increased markedly with age being 33 per cent in patients aged 40 to 49 38 per cent in those aged 50 to 59, 64 per cent in those aged 60 to 69 and 76 per cent in those over 70 years of age (Fig 1) The corresponding figures for the 156 surgical patients were 27, 38 61, and 74 per cent The corresponding figures for the 87 surgical cases in 1973 assuming normal coronary vessels in those not studied by coronary arteriography were 0, 12 55 and 60 per cent Thus any figure given for the over all incidence must depend heavily on the age composition of the group in question

There was no over all difference according to sex, coronary disease occurring in 60 per cent of women and 56 per cent of men The incidence was 63 per cent (5 of 8) in women aged 60 to 69 and [illegible] per cent (9 of 12) in women aged 70 and over Only five women under age 60 were studied and only one of these had significant coronary disease a woman aged 42 who had severe type II hypercholesterolemia, multiple previous myocardial infarctions with a ventricular aneurysm and moderate aortic stenosis Thus it seems likely that women under age 60 with aortic stenosis have a lower prevalence of coronary disease than do men of the same age, but the number studied is too small to permit a firm conclusion

The distribution of coronary occlusive lesions among the four principal coronary arteries is given in Table II The left anterior descending artery was the vessel most frequently involved and combinations involving two or three major vessels were more frequent than single vessel involvement, as is observed in coronary artery disease generally Marked obstruction of the left main coronary artery occurred in 10 patients all of whom had multivessel disease The lesions were at the left coronary ostium in three of these patients Right coronary ostial lesions of significant degree were identified in six patients and in two these were the only coronary lesions present Calcification of the left main coronary artery was noted in 27 patients only two of whom showed significant obstruction of that artery, but 21 of them had lesions elsewhere in the proximal coronary arteries

Table II Distribution of significant coron[illegible] occlusive lesions in 97 patients

	No
Single lesions	
LAD	11
LCCA	3
RCA	14
Double lesions	
LMCA–LAD	1
LAD–LCCA	14
LAD–RCA	14
RCA–LCCA	6
Triple and quadruple lesions	
LMCA–LAD–LCCA	1
LMCA–LAD–RCA	1
LMCA–LCCA–RCA	1
LAD–LCCA–RCA	6
LMCA–LAD–LCCA–RCA	5

Abbreviations LAD = left anterior descending coronary artery LCCA = left circumflex coronary artery RCA = right coronary artery LMCA = left main coronary artery

Table III The number of patients with each of four types of chest pain syndromes according to the severity of occlusive lesions found on coronary arteriography

Severity of coronary disease	*AS type angina*	*CAD type angina*	*Nonanginal chest pain*	*No pain*
0	1	8	5	14
+	15	6	3	8
++	10	12	1	1
+++	16	44	5	8

AS-type refers to angina pectoris which occurs only with physical exertion and in association with dyspnea on exertion or in a few instances during paroxysmal tachyarrhythmias as well. CAD type refers to angina pectoris which occurs on exertion but without dyspnea on exertion or which also occurs with emotional stress after meals or at rest including nocturnal angina. Abbreviations are as given in Table II.

Total occlusions occurred in 26 arteries in 24 patients involving the left anterior descending artery alone in two the left circumflex artery alone in four the right coronary artery alone in 16 and in one patient each the left anterior descending and right arteries and the left circumflex and right arteries All but one of the patients with total occlusion had significant lesions in other arteries and this patient possibly had a congenitally hypoplastic right coronary artery rather than an acquired total occlusion

Patients with angina pectoris had significant coronary lesions in 64 per cent of instances compared with 33 per cent in patients with no angina ($P = < 0.01$) This varied with age coronary lesions being found in 45 per cent of patients aged 40 to 49 with angina 46 per cent aged 50 to 59 69 per cent aged 60 to 69 and 86 per cent of those 70 years of age or more

Patients with significant coronary disease in the absence of angina were over the age of 60 in 12 of 15 instances All were men In nine of them there was no history of chest pain at all whereas six described chest pains of varying types considered to be nonanginal Among those with no chest pain one had myocardial infarction documented in past ECG s one developed angina for the first time during an episode of paroxysmal tachycardia during cardiac catheterization and one had a peculiar history of acute dyspneic attacks on exertion which had been considered an anginal equivalent by the referring physician One patient with no chest discomfort related to effort or other stress did have occasional episodes of

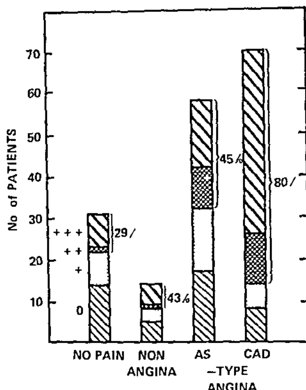


Fig 2 The incidence of coronary artery disease in 173 patients with aortic stenosis according to the type of chest pain syndrome described (see text) Significant coronary disease (++ or +++) is more frequent in those with CAD type angina than in those with AS-type angina nonanginal pain or no pain ($P = < 0.01$ for each comparison) The incidence of coronary disease is not significantly higher in those with AS type angina than in those with nonanginal pain or no pain

prolonged pain consistent with episodic coronary insufficiency Congestive heart failure was the principal presenting problem in seven of these patients dyspnea on exertion in three effort syncope in four and complete heart block with syncope in one

The histories of chest pain were divided into four categories (Table III) Angina pectoris which occurred only on exertion and only in association with dyspnea on exertion was associated with significant coronary lesions in 45 per cent of instances Angina which occurred without dyspnea or which occurred at rest after meals during sleep or with emotional stress was associated with coronary disease in 80 per cent of instances a statistically significant difference ($P = < 0.01$) Patients with nonanginal chest pain had coronary disease in 43 per cent of instances while those with no history of chest pain at all had coronary disease in 29 per cent of

Table IV The number of patients with various ECG patterns according to the severity of occlusive lesions found by coronary arteriography

Severity of coronary disease	*No pathologic Q waves*	*QS in V₁ V₂ only*	*Anterior infarct*	*Inferior infarct*	*Anterior and inferior infarct*
0	35	4	1	0	0
+	24	5	0	1	0
++	16	5	0	2	0
+++	39	11	4	9	5

instances These differences are illustrated in Fig 2 where the first type of angina is called AS type and the second is called CAD type angina

A history of hospitalization for suspected acute myocardial infarction in the past was noted in 43 per cent of the 173 patients, but this diagnosis had been made following the in hospital observation in only 23 per cent and was confirmed by typical transmural infarction patterns in the ECG in only 5 per cent The corresponding figures for those with significant coronary disease were 54, 34, and 9 per cent whereas they were 29 11 and 0 per cent in those with no significant coronary lesions

An analysis of the ECG evidence of myocardial infarction as noted at the time of preoperative angiographic study is presented in Table IV QS patterns in Lead V_1 or in Leads V_1 and V_2 without other evidence of infarction occurred with nearly equal frequency in patients with and without significant coronary disease Infarction patterns represented by pathologic Q waves in Leads V_{4-6} or II, III and a V_F were on the other hand associated with coronary disease in 20 of 22 instances There was a history of suspected acute myocardial infarction in the past in nine of these patients, documented by characteristic ECG changes at the time in five One patient diagnosed as having anterior infarction electrocardiographically with normal coronary arteriography had marked left axis deviation with QRS pattern in Lead V_{1-2}, a pattern possibly attributable to left anterior fascicular block rather than infarction there was no history suggestive of acute myocardial infarction in the past One patient with an inferior infarct pattern had a distal right coronary artery which was small irregular, and not optimally seen, and may well have contained occlusive disease related to the infarction, he had a history of suspected acute myocardial infarction in the past

The coronary artery whose distribution corresponded to the area of infarction indicated in the ECG showed significant occlusive disease in all patients except the two mentioned above and showed complete occlusion in nine of 22 Among the 12 patients with inferior infarction pattern, there were five with total occlusion of the right coronary artery Two additional patients with inferior infarction patterns in past ECGs which had later resolved to within normal range showed in one instance total occlusion of the left circumflex artery with minor disease of the right coronary artery and in the other severe triple vessel disease with no total occlusions No total occlusions were present in the five patients with anterior infarction patterns, whereas in five patients with patterns of both anterior and inferior infarction one showed total occlusion of the right coronary artery and one showed total occlusion of both the right coronary and left anterior descending coronary arteries Two patients had complete left bundle branch block patterns, with past ECG's showing infarction before the development of bundle branch block anterior in one and inferior in the other, both had total occlusion of the right coronary artery with significant left sided lesions as well

Complete left bundle branch block was present in nine patients over all four with significant coronary disease and five without all but one were over 60 years of age Complete right bundle branch block was present in six patients four with significant coronary disease and two without, all but one of these also were over 60 years of age Second or third degree atrioventricular block which was persistent and led to permanent pacemaker insertion prior to aortic valve replacement occurred in four patients, two aged 67 and 79 years with severe coronary disease and two aged 69 and 77 years with no significant coronary disease

Five patients had atrial fibrillation three with significant coronary disease and two without Two of the five were women and all were 67 to 70 years of age Three additional patients had marked sinus bradycardia with predominantly atrioventricular junctional rhythm each with minimal coronary disease Two of the three were women, and all were 66 to 76 years of age

Hemodynamic data in patients with and

Table V The number of patients with normal and elevated serum lipids according to the severity of occlusive coronary lesions found by coronary arteriography

Severity of coronary disease	*Serum cholesterol*		*Serum triglyceride*	
	Normal	*Elevated*	*Normal*	*Elevated*
0	40	[illegible]	17	5
+	[illegible]	4	13	4
++	[illegible]	[illegible]		[illegible]
+++	49	19	20	15

Table VI The number of patients with various patterns on lipoprotein electrophoresis according to the severity of occlusive lesions found by coronary arteriography

Severity of coronary disease	*Normal*	*IIa*	*IIb*	*IV*
0	16	0	0	5
+	11	[illegible]	0	5
++	[illegible]	0	2	5
+++	1	4	4	10

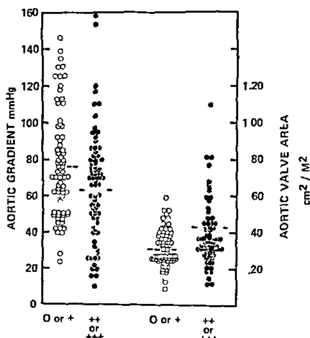


Fig 3 Hemodynamic data in 173 patients with aortic stenosis divided into those with (++ or +++) or without (0 or +) significant associated coronary artery occlusive lesions. Aortic gradient is the peak to peak transaortic valvular systolic pressure gradient at rest Horizontal dashed lines indicate the mean value for each group

without significant coronary disease are given in Fig 3 Coronary disease was somewhat less frequent in the patients with transaortic systolic pressure gradients in excess of 100 mm Hg (35 vs 59 per cent) but this difference was not statistically significant Coronary disease was however markedly more frequent in those with pressure gradients under 40 mm Hg (18 of 20 instances) (P = < 0 01) One patient with a gradient under 40 mm Hg with no significant coronary disease was aged 69 and may actually have had diffuse coronary disease since the arteries appeared generally small particularly the right coronary artery and were felt to be diffusely sclerotic at the time of operation The other patient was aged 77 and had a very small short right coronary artery with posterior wall akinesis in the left ventricular cineangiogram The aortic valve area was less than 0 55 cm ² per square meter in all patients without coronary disease with one exception at 0 59 cm ² per square meter with minimal symptoms while 12 patients with combined aortic stenosis and coronary disease had valve areas in the range of 0 55 to 0 80 cm per square meter or in one instance 1 1 centimeter squared per square meter as was mentioned previously

The 12 patients with aortic valve area greater than 0 55 cm ² per square meter associated with coronary disease all had angina and in 11 of 12 instances had angina as their sole or chief presenting clinical problem The anginal syndrome included features other than pure effort angina dyspnea in 11 of 12 instances Three had documented previous myocardial infarctions Combined aortic valve replacement and coronary artery bypass surgery was done in six coronary bypass alone in two and aortic valve replacement alone in only one One died awaiting surgery one declined coronary bypass surgery and one was considered inoperable because of an excessively large left ventricular aneurysm with total occlusion of the right coronary and left anterior descending coronary arteries These patients thus appeared to have coronary artery disease predominantly with a lesser degree of aortic stenosis which perhaps contributed relatively little to the symptoms and clinical course in some of them

Serum lipid values are given in Table V Serum cholesterol was determined in 166 patients and 86 of these also had determination of serum trigly

Table VII The number of patients with various coronary risk factors according to the severity of occlusive lesions found by coronary arteriography

Severity of coronary disease	*Total no*	*Family history of coronary disease*	*Hypertension*	*Cigarette smoking*	*Diabetes*	*Peripheral vascular disease*
0	44	8	9	17	2	2
+	32	7	11	15	3	0
++	24	7	11	13	1	1
+++	73	33	18	34	8	11

Table VIII The number of patients with various coronary risk factors present according to the severity of occlusive lesions found by coronary arteriography

Severity of coronary disease	*No of coronary risk factors present**					
	0	*1*	*2*	*3*	*4*	*5*
0	12	22	9	1	0	0
+	8	12	7	3	2	0
++	5	6	7	4	2	0
+++	9	26	22	8	6	2

*The risk factors include hyperlipidemia hypertension smoking diabetes peripheral vascular disease and a family history of coronary artery disease

ceride and lipoprotein electrophoretic pattern Serum cholesterol was elevated in 23 per cent of those with significant coronary disease compared with only 8 per cent of those without significant disease (P = < 0 05) The corresponding figures for triglyceride level were 45 and 24 per cent (P = < 0 05), and for elevation of either or both serum lipids the figures were 51 and 29 per cent

The distribution of lipoprotein types is given in Table VI The incidence of hypertriglyceridemia and abnormal electrophoretic patterns may be over estimated somewhat since these determinations were done more frequently in those with elevated serum cholesterol than in those with normal cholesterol (69 vs 50 per cent)

In addition to hyperlipidemia, patients with significant coronary disease had somewhat greater frequency of diabetes, cerebral or peripheral occlusive vascular disease and family histories of coronary disease, and slightly greater frequency of hypertension and cigarette smoking (Table VII), however, only the family history of coronary disease was statistically significant A multiplicity of these risk factors was also significantly more frequent in patients with coronary disease (Table VIII)

The relation of coronary disease to operative deaths at the time of aortic valve replacement was as follows There were 19 deaths within 30 days after operation in the total group of 304 surgical patients over a 4 year period (6 2 per cent), with figures of 8 7, 6 3 5 8, and 4 7 per cent for the four successive years Four of these deaths occurred in patients who had suffered cardiac arrest in the hospital, in whom the aortic valve replacement was performed as part of an unsuccessful resuscitative effort The operative mortality rates excluding these cases were 8 7, 5 1, 3 0 and 3 5 per cent for the 4 successive years Coronary arteriography had been done preoperatively in nine of the patients who died and showed severe coronary disease in eight Postmortem examination showed severe coronary disease in at least three of six who did not have arteriography and who died postoperatively and in two of the four with unsuccessful surgery performed after cardiac arrest Thus significant coronary disease was present in at least 74 per cent of these fatal cases Coronary artery bypass surgery was combined with aortic valve replacement in six of the eight patients who died after operation with an abnormal coronary arteriogram preoperatively Combined coronary artery bypass and aortic valve replacement were carried out in a total of 56 patients in this series with an 11 per cent operative mortality rate, compared with a 5 per cent operative mortality rate in the 248 patients who had aortic valve replacement alone The operative mortality rate was 7 per cent (two of 27) in those in whom only aortic valve replacement was carried out although significant coronary lesions were demonstrated preoperatively There was only one operative death among 73 patients who

had a normal coronary arteriogram preoperatively (1 4 per cent)

The 16 patients who did not have aortic valve replacement for various reasons included four who died unexpectedly during the interval between the time of cardiac catheterization and angiography and the scheduled operation Severe coronary disease was present in three of these patients who were 66 73 and 75 years of age Two experienced sudden deaths of cardiac nature but one developed a hemorrhagic colitis of either ischemic or ulcerative nature and died following colectomy

Discussion

This study confirms the substantial prevalence of severe coronary artery disease in patients with calcific aortic stenosis found in previous arteriographic and pathological studies It goes beyond previous studies in indicating the greater prevalence in patients in the older age groups and in those with angina pectoris particularly the type of angina described here as CAD type

The 15 patients who had significant coronary disease without angina pectoris are an important group in view of the suggestions that this is very unlikely to occur[3] The male patient over 60 years of age presenting with congestive heart failure appears to be particularly likely to show coronary disease without angina This may simply reflect the general clinical observation that angina pectoris tends to be absent when congestive heart failure develops perhaps because physical activity becomes limited Coronary disease without angina also occurred in patients in whom effort syncope was the only complaint and in whom left ventricular function was very well preserved The vasodepressor reflex theory of syncope in aortic stenosis[5] would help to explain this since no decompensation or defect in left ventricular function is postulated and patients with syncope alone may be regarded as presymptomatic as far as left ventricular function is concerned The same would be true of patients symptomatic only because of heart block causing syncope

The observation of a different type of angina in patients with aortic stenosis alone from that in those with aortic stenosis associated with coronary artery disease stemmed from an earlier observation that patients with aortic stenosis over the age of 40 virtually always show an abnormal rise in left ventricular diastolic and pulmonary venous pressures during exercise[48] It appeared from this that a degree of aortic stenosis sufficient to cause angina should as a rule result in dyspnea on exertion as well due to the rise in pulmonary venous pressures Patients with angina due to coronary artery disease on the other hand frequently have no rise in pulmonary venous pressure during exercise[9] and frequently have no dyspnea in association with their angina Indeed Heberden[50] commented on this in his classical description of angina In all other respects the patients are at the beginning of this disorder perfectly well and in particular have no shortness of breath from which it is totally different

It is also possible that the CAD type angina simply represents a more severe degree of myocardial ischemia than that which occurs on the basis of aortic stenosis alone Or another speculation may be that in the presence of coronary artery disease changes in the degree of coronary vasoconstriction are contributory to the precipitation of angina by circumstances other than physical exertion

Myocardial infarction has been noted at post mortem examination in some patients with aortic stenosis without coronary disease [9, 51, 53] but this is not very frequent It has also been noted from a clinical point of view that acute myocardial infarction with a typical transmural ECG pattern is quite rare in the presence of aortic stenosis[3, 1, 54, 56] unless coronary disease is also present Occasional instances of infarction may result from embolism of calcific fragments from the aortic valve into the coronary arteries[57, 5] The myocardial infarction which occurs in young patients with severe congenital aortic stenosis is primarily of a diffuse subendocardial and papillary muscle location[60, 61] Thus the high specificity of ECG infarction patterns for associated coronary disease found in the present study indicates a very useful diagnostic point

The observation that left ventricular hypertrophy alone is a cause of QS patterns in Leads V_1 and V_2[6, 4] was borne out in this study Similarly, patterns of right or left bundle branch block and atrioventricular block in patients with aortic stenosis are apparently on the basis of left ventricular hypertrophy or of fibrotic or calcific

degenerative changes in the specialized conducting tissues rather than associated coronary disease, at least in most instances

The pathologic process in calcific aortic stenosis is similar to that in atheromatous disease of the coronary arteries with lipid deposition occurring at a very early stage,[65] followed later by the development of gross calcific masses It is reasonable to consider whether elevations of serum cholesterol and triglyceride might play the same accelerating role in aortic stenosis as they are thought to do in coronary artery disease, although little attention has been given to this in the literature Boas and associates[56] noted a slightly increased incidence of hypercholesterolemia in patients particularly women, with calcific aortic stenosis and espoused the concept of a common etiology between aortic stenosis and the usual forms of degenerative vascular disease Patients with familial hypercholesterolemia frequently show some aortic valve thickening on the basis of xanthomatous deposition in the leaflets,[56, 66-71] but there is little to indicate that severe aortic stenosis occurs with increased frequency in these patients[72, 75] The rare instances of severe aortic stenosis in young patients with the homozygous form of familial hypercholesterolemia when studied with modern methods appear to be instances of acquired supravalvular stenosis due to xanthomatous masses in the aortic wall[76-78] rather than severe valvular stenosis The incidence of hyperlipidemia in the present series of patients without coronary disease appears to be not significantly higher than that found in the general population in this country,[79, 80] and the coronary risk factors appear to have much the same predictive value for coronary disease in patients with aortic stenosis as in the population generally

The combined operation of aortic valve replacement and coronary artery bypass grafting can be done with a reasonable operative risk and good clinical results[30, 41] The view is now widely held that patients with aortic stenosis and angina pectoris should have coronary arteriography preoperatively to permit the combined operation to be done if necessary[81] Probably this is particularly important when the aortic stenosis is only moderate in severity, since in such cases the symptoms are more likely to be due to the coronary disease The present study indicates that if the aortic valve area is greater than 0.75 cm² per square meter, angina is very unlikely to be due to aortic stenosis alone

The presence of significant coronary artery disease is clearly of predictive value with regard to the operative mortality rate in aortic valve replacement for aortic stenosis, even though it is not clear yet whether performance of coronary artery bypass simultaneously will reduce this figure It is also not clear yet whether coronary artery bypass in combination with aortic valve replacement improves the long term clinical results in patients with aortic stenosis without angina Thus it remains debatable whether all patients should have coronary arteriography prior to surgery for aortic stenosis The findings in the present study, indicating that a combination of clinical features will permit a prediction of coronary disease in many instances, should be helpful in guiding a selection of patients for coronary arteriography until such time as answers to the above questions are evolved If a selective policy is followed, coronary arteriography should be done particularly in patients who are over 60 years old those who have angina pectoris of CAD type, and those with symptoms despite only moderate aortic stenosis Similar recommendations have been made recently by Henlin and associates[82]

Summary

The relationships between aortic stenosis coronary artery disease, angina pectoris and myocardial infarction were examined in 173 patients with isolated calcific aortic stenosis who had coronary arteriography as well as cardiac catheterization All were over age 40 and had definite cardiac symptoms 156 later had aortic valve replacement Coronary lesions narrowing the lumen by 50 per cent or more were present in 37 per cent of patients aged 40 to 59 and 68 per cent of those aged 60 to 82 Coronary disease was present in 64 per cent of patients with angina pectoris and 33 per cent of those without angina Angina which occurred only in association with dyspnea on exertion was associated with coronary disease in 45 per cent of instances, whereas angina which also occurred on exertion without any dyspnea or which occurred with emotional stress after meals during sleep, or at rest unprovoked was associated with coronary disease in 80 per

cent of instances Patients with coronary disease without any chest pain or with atypical pain considered nonanginal were men usually over age 60 with congestive heart failure as the predominant symptom Electrocardiograms showing *transmural inferior or anterolateral infarction* nearly always indicated coronary disease while QS patterns in Leads $V_{1,2}$ occurred frequently with normal coronary arteries Serum cholesterol was elevated in 23 per cent of those with coronary disease and 8 per cent of those without A group of *patients* with moderate aortic stenosis could be identified with aortic valve areas of 0 55 to 0 80 cm per square meter in whom coronary disease was the sole or chief cause of symptoms The operative mortality rate with aortic valve replacement was 9 6 per cent in those with coronary disease and 1 4 per cent in those without significant coronary disease Coronary disease is frequently present in patients with calcific aortic stenosis particularly in those over 60 those with angina and those with symptoms despite only moderate aortic stenosis The type of anginal syndrome the ECG evidence of transmural infarction and the coronary risk factors provide additional clues for clinical diagnosis

REFERENCES

1 Cabot R C Facts on the heart Philadelphia 1926 W B Saunders Company 1926 pp 205 766

2 Christian H A Aortic stenosis with calcification of the cusps Distinct clinical entity J A M A 97 158 1931

3 Margolies, H Ziellesson F O and Barnes A R Calcareous aortic valvular disease AM HEART J 6 349 1931

4 Dry T J and Willius F A Calcareous *disease of the* aortic valve A study of 2 8 cases AM HEART J 17 138 1939

5 Lesnick H and Schlesinger M J Calcareous aortic stenosis AM HEART J 16 43 1938

6 Friedberg C K and Horn H Acute myocardial infarction not due to coronary occlusion J A M A 112 1675 1939

7 Ashworth C T Atherosclerotic valvular disease of the heart Arch Pathol 42 285 1946

8 Horan M J Jr and Barnes A R Calcareous aortic stenosis and coronary artery disease Am J Med Sci 215 451 1948

9 Kumpe C W and Bean W B Aortic stenosis A study of the clinical and pathological aspects of 107 proved cases Medicine 27 139 1948

10 Anderson M W Kelsey J R Jr and Edwards J E Clinical and pathological considerations in cases of calcific aortic stenosis J A M A 149 9 1952

11 Wood, P Aortic stenosis Am J Cardiol 1 553 1958

12 Abelmann W H and Ellis L B Severe aortic stenosis in adults Evaluation by clinical and physiologic criteria and results of surgical treatment Ann Intern Med 51 449 1959

13 Dexter L Harken D E Cobb L A Jr Novack P, Schlant R C Phinney A O Jr and Haynes F W Aortic stenosis Arch Intern Med 101 254 1958

14 Hancock E W, and Fleming P R Aortic stenosis Q J Med 29 209 1960

15 Baker C and Somerville J Clinical features and surgical treatment of fifty patients with severe aortic stenosis Guys Hosp Rep 108 101 1959

16 Braunwald, E., Roberts W C Goldblatt A Aygen M M and Rockoff S D Aortic stenosis Physiological pathological, and clinical concepts Ann Intern Med 58 494 1963

17 Scannell J G and Austen W G Operative treatment of aortic stenosis in the elderly patient N Engl J Med 270 96 1964

18 Bowles, L T Hallman G L and Cooley D A Open heart surgery in patients over sixty years of age *J Am* Geriatr Soc 17 817 1969

19 Finegan R E Gianelly R E and Harrison D C Aortic stenosis in the elderly Relevance of age to diagnosis and treatment N Engl J Med 281 1261 1969

20 Austen W G DeSanctis R W., Buchler M J Mundth E D and Scannell J G Surgical management of aortic valve disease in the elderly J A M A 211 624 1970

21 Shanahan M X Windsor H M and Golding L Open heart surgery in the elderly Aust N Z J Surg 42 107 1972

22 Oh W Hickman R., Emanuel, R McDonald L Somerville J Ross D Ross K and Gonzales-Levin L Heart valve surgery in 114 patients over the age of 60 Br Heart J 35 174 1973

23 Linhart J W de la Torre A Ramsey H W and Wheat M W Jr The significance of coronary artery disease in aortic valve replacement *J Thorac Cardio*vasc Surg 55 811 1968

24 Elliott W C Cohen L S Klein M D Lane F J., and *Gorlin R* Selective cinearteriographic study of angina pectoris in valvular heart disease Circulation 30 (Suppl *III*) *III 73 1964*

25 Nakib A Lillehei C W and Edwards J E The degree *of coronary* atherosclerosis in aortic valvular disease Arch Pathol 80 517 1965

26 Storstein O and Efskind, L Aortic stenosis diagnosis and surgical treatment Cardiologia *49 259 1966*

27 Tala P Salonen I S and Rissanen K The pathoanatomical basis of aortic valve *replacement* Autopsy observations of 100 unselected cases Ann Chir Gynae col Fenn 57 184 1968

28 Bjork L and *Cullhed I* Coronary arteriography in valvular heart disease Acta Med Scand 185 531 1969

29 Coleman E H and Soloff L A Incidence of significant coronary disease in rheumatic valvular *heart* disease Am J Cardiol 25 401 1970

30 Flemma R J Johnson W D *Lepley D Jr* Auer J E Tector A J and Blitz J Simultaneous valve replacement *and aorta* to-coronary vein bypass Ann Thorac Surg 12 163 1971

31 Loop F D Favaloro R G Shirey E K Groves L K., and Effler D B Surgery for combined valvular and coronary heart disease J A M A *220 372 19 2*

32 *Mer*n *G* Danielson G K Wallace R B., Rutherford B D and Pluth J R Combined one stage coronary artery and valvular surgery—A clinical evaluation Circu*lation* 48 (Suppl III) III 173 1973

33 Morris G C., Howell, J F., Crawford, E S Reul, G J

and Stelter W Operability of end stage coronary artery disease Ann Surg 175 1024 1972
34 Hall R J Dawson J T Cooley D A Hallman G L Winkasch D C and Garcia F Coronary artery bypass Circulation 48 (Suppl III) III 146 1973
35 Hutchinson J E Green G E Makhjian H A and Kemp H G Aortic valve replacement combined with coronary bypass grafts long term results N Y J Med 73 1299 1973
36 Skow J R Carey J S Plested W G III and Mulder D G Saphenous vein bypass as a secondary procedure Arch Surg 107 34 1973
37 Berndt T B Hancock E W Shumway N E and Harrison D C Aortic valve replacement with and without coronary artery bypass surgery Circulation 50 967 1974
38 Sandiford F M Reul G J Winkasch D C Chiariello L Hallman G L and Cooley D A Aortic valve replacement with concomitant aortocoronary bypass (abst) Am J Cardiol 33 168 1974
39 Anderson R P Bonchek L I Wood J A Chapman R P and Starr A The safety of combined aortic valve replacement and coronary bypass grafting Ann Thorac Surg 15 249 1973
40 Bonchek L I Anderson R P and Rosch J Should coronary arteriograms be performed routinely prior to valve replacement? Am J Cardiol 31 462 1973
41 Cooley D A Dawson J T Hallman G L Sandiford F M Winkasch D C Garcia E and Hall R J Aortocoronary saphenous vein bypass Results in 1492 patients with particular reference to patients with complicating features Ann Thorac Surg 16 380 1973
42 Gorlin R and Gorlin S G Hydraulic formula for calculation of the area of the stenotic mitral valve other cardiac valves and central circulatory shunts Am Heart J 41 1 1951
43 Lewis T Diseases of the heart ed 4 London 1948 MacMillan Company p 66
44 Levine S A Clinical heart disease ed 5 Philadelphia 1958 W B Saunders Company p 117
45 Johnson A M Aortic stenosis sudden death and the left ventricular baroceptors Br Heart J 33 1 1971
46 Mark A L Kioschos J M Abboud F M Heistad D D and Schmid P G Abnormal vascular responses to exercise in patients with aortic stenosis J Clin Invest 52 1138 1973
47 Mark A L Abboud F M Schmid P G and Heistad D D Reflex vascular responses to left ventricular outflow tract obstruction and activation of ventricular baroceptors in dogs J Clin Invest 52 1147 1973
48 Hancock E W Hemodynamics during exercise in aortic stenosis Circulation 46 (Suppl II) II 165 1972
49 Goldschlager N Sakai F J Cohn K E and Selzer A Hemodynamic abnormalities in patients with coronary artery disease and their relationship to intermittent ischemic episodes Am Heart J 80 610 1970
50 Heberden W Commentaries on the history and cure of diseases Boston 1818 Wells & Lilly
51 Bergeron J Abelmann W H Vasquez Milan H and Ellis L B Aortic stenosis Clinical features and course of the disease Arch Intern Med 94 911 1954
52 Duke M and Eddy J R Aortic stenosis and trans mural myocardial infarction without coronary artery disease Angiology 21 265 1970
53 Falase A O Cole T O and Osuntokun B O Myocardial infarction in Nigerians Trop Geogr Med 25 147 1973
54 Anderson M W The clinical course of patients with calcific aortic stenosis Proc Staff Meet Mayo Clin 36 439 1961
55 DeSanctis R W Question and answers—can aortic stenosis cause myocardial infarction? J A M A 205 1968
56 Boas E P Elster S K and Adlersberg D Calcific aortic stenosis Study of serum cholesterol Am Heart J 48 485 1954
57 Moragnes V Bawell M B and Shrader E L Coronary embolism Review of literature and report of unique case Circulation 2 434 1950
58 Lillington G A Connally D C and Kavanaugh G J Coronary embolism secondary to subacute bacterial endocarditis in a case of calcific aortic stenosis Circulation 33 216 1958
59 Kavanaugh G J Pruitt R D and Edwards J E Coronary embolism and cystic medial necrosis of ascending aorta associated with calcific aortic stenosis Proc Staff Meet Mayo Clin 33 222 1958
60 Kangos J J Ferrer M I Franciosi R A Blanc W A and Blumenthal S Electrocardiographic changes associated with papillary muscle infarction in congenital heart disease Am J Cardiol 23 801 1969
61 Vinant W R Buckberg E D and Hoffman J I E Left ventricular subendocardial ischemia in severe valvular and supravalvular aortic stenosis A common mechanism Circulation 49 396 1974
62 Hugenholtz P G Ryan T J and Woener T Recognition of anterior wall infarction in patients with left ventricular hypertrophy Circulation 27 386 1963
63 Marriott H J L Practical electrocardiography ed 4 Baltimore 1968 The Williams & Wilkins Company p 198
64 Beamer V Amidi M and Scheuer J Vectorcardiographic findings simulating myocardial infarction in aortic valvular disease J Electrocardiol 3 71 1970
65 Hultgren H N Calcific disease of the aortic valve Arch Pathol 45 694 1948
66 Cook C D Smith H L Giesen C W and Bendez G L Xanthoma tuberosum aortic stenosis coronary sclerosis and angina pectoris Am J Dis Child 73 3?? 1947
67 Barr D P Rothbard S and Eder H A Atherosclerosis and aortic stenosis in hypercholesterolemic xanthomatosis J A M A 156 943 1954
68 Harris-Jones J N Jones E G and Wells P G Xanthomatosis and essential hypercholesterolemia Lancet 1 855 1957
69 Rigdon R H and Willeford G Sudden death during childhood with xanthoma tuberosum J A M A 142 1268 1950
70 Khachadurian A K The inheritance of essential familial hypercholesterolemia Am J Med 37 402 1964
71 Rothbard S Hagstrom J W S and Smith J P Aortic stenosis and myocardial infarction in hypercholesterolemic xanthomatosis Am Heart J 73 687 1967
72 Thannhauser S J Lipidoses Disease of the cellular lipid metabolism ed 3 New York 1958 Grune & Stratton Inc p 124
73 Schettler F G Essential familial hypercholesterolemia in Schettler F G and Boyd G S Atherosclerosis Amsterdam 1969 Elsevier Publishing Company p 543
74 Goldstein J L The cardiac manifestations of familial type II homozygous and heterozygous forms of familial type II hyperbetalipoproteinemia Birth Defects 8 207 1972
75 Stone N J Levy R I Fredrickson D S and Verter J Coronary artery disease in 116 kindred with familial

type II hyperlipoproteinemia Circulation **49** 476 1974

Stanley P Chartrand C and Davignon A Acquired aortic stenosis in a twelve year old girl with xanthomatosis. Successful surgical correction N Engl. J Med **273** 1378 1965

Buchwald H Lee G B Amplatz K Moore R B Frantz, I D Jr and Varco R L. Severe atherosclerotic cardiovascular disease in a 14 year old homozygous familial hypercholesterolemic Minn Med **51** 477 1968

Wennevold, A and Jacobsen J G Acquired supravalvular aortic stenosis in familial hypercholesterolemia Am J Med **50** 823 1971

Wood P D S Stern M P Silvers A Reaven G M and Von der Groeben J Prevalence of plasma lipoprotein abnormalities in a free living population of the Central Valley California Circulation **45** 114 19 2

80 Ostrander L D Lamphiear D E., Block, W D., Johnson B C and Epstein F H Biochemical precursors of atherosclerosis Studies in apparently healthy men in a general population Tecumseh Mich. Arch Intern Med **134** 225 1974

81 Kasparian H., Duca P R Goodman S Wiener L and Brest A N The diagnosis and management of obstructive coronary disease in patients with significant chronic valvular disease Cardiovasc Clin **5** 307 1973

82 Henlin A Joffe G., Audoin J Delarue F Guillemot R Vacheron A., and DiMatteo J Retricissement aortique calcifie et atherosclerose coronarienne Arch Mal Coeur **66** 1381 1973

Beta-adrenergic blockade in hypertension

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Treatment of arterial hypertension with beta adrenergic blocking agents has become increasingly common in many countries during the last few years In several European centers beta adrenergic blockers have even superseded diuretics as the first drug of choice when starting treatment in previously untreated hypertension

Much research has gone into this field e g, in order to clarify the antihypertensive mechanism of these agents Moreover the number of drugs with beta receptor blocking effects that are available for the treatment of hypertension has increased successively during the last years The present review is an attempt to cover some of the aspects on the use of beta adrenergic blockers in the therapy of hypertension seen against this background

During the few decades in which meaningful antihypertensive therapy has been available a few important milestones are easily recognizable at which significant improvements of therapy have resulted, e g, the introduction of the ganglionic blocking agents the availability of reserpine, or the development of thiazide diuretics in the 1950's The recent introduction of beta adrenergic blocking agents in the therapy of hypertension could be regarded as the latest step in this development

The first reports that beta blockers lowered blood pressure in hypertensive patients were published in 1964 by Schroder and Werko[1] and Prichard and Gillam[2] During the following years a number of studies have confirmed these initial reports using propranolol[3-11] alprenolol[12-16] practolol,[17, 18] pindolol[19] oxprenolol[20] and timolol[19]

A contributing reason for the increasing use of these agents has been their relative lack of serious side effects provided that contraindications such as obstructive respiratory disease and impending heart failure have been observed

It has also been considered an important advantage that postural or exercise hypotension as seen with sympatholytic agents do not occur during treatment with beta adrenergic blocking agents[5, 8]

Furthermore, there is no doubt that considerable reductions of raised blood pressure can be achieved during treatment with beta blockers Thus, the antihypertensive effect of propranolol has been reported as being at least as potent as that of e g, guanethidine[5, 10] In long term treatment almost 80 per cent of patients reacted favorably to the use of propranolol[10]

Pharmacological properties

Propranolol and most of the other beta adrenergic blocking agents that are clinically available in many countries today could be regarded as first generation beta blockers Thus these agents block beta 1 receptors e g in the myocardium as well as beta 2 receptors e g in the bronchi or peripheral blood vessels As illustrated in Table I many of these agents also have a membrane stabilizing effect which is sometimes referred to as a quinidine like or local anesthetic action This also implies some myocardial depression The importance of the membrane stabilizing effect should not be exaggerated however in the ordinary clinical use of these drugs Even with the comparatively high doses of beta blockers that are frequently used in hypertension this effect hardly has to be taken into account as approximately 100 times higher dosage is needed to demonstrate it in comparison with the dosage needed to demonstrate beta receptor blockade[1]

Some of the beta adrenergic blocking agents

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also have a sympathomimetic action (Table I). This could be simply described as a weak agonist action of the compound in addition to its antagonistic action. In the clinical situation, beta blockers with sympathomimetic effect could be expected to cause a lesser reduction of resting heart rate and myocardial performance than agents devoid of this characteristic.

During the last few years more specific beta blocking agents have appeared. This second generation of beta adrenergic blocking agents could be characterized as being cardioselective in their action since they block beta 1 receptors specifically. Practolol, metoprolol, atenolol, and tolamolol (Table I) are all specific beta 1 receptor blockers. Their specificity for beta 1 receptors is not absolute, however, but the affinity for blocking beta 1 receptors is 50 times higher or more than the effect on beta 2 receptors. Clinically this means that patients with obstructive respiratory disease could be treated with considerably less risk of producing bronchoconstriction.

Table I Pharmacological properties of some beta receptor antagonists

	Blockers		*Sympathomimetic effect*	*Membrane stabilizing effect*
	Beta 1	*Beta 2*		
Propranolol	+	+	—	+
Alprenolol	+	+	+	+
Oxprenolol	+	+	+	+
Sotalol	+	+	—	—
Timolol	+	+	—	—
Penbutolol	+	+	—	+
Pindolol	+	+	+	+
Practolol	+	—	+	—
H 93/26 metoprolol	+	—	—	—
ICI 66 082 atenolol	+	—	—	—
Tolamolol	+	—	—	—

Antihypertensive mechanisms

From the onset of beta receptor blocking therapy in hypertension, great interest has been focused on possible mechanisms underlying the antihypertensive action. In brief, hemodynamic mechanisms, central nervous actions, renin angiotensin effects, as well as effects related to the local anesthetic effect have been discussed in this connection.

Hemodynamic effects. It is well known that most forms of established hypertension are characterized by normal cardiac output and elevated total peripheral resistance. Therefore it could seem unlogical to administer beta adrenergic blocking agents in this condition in view of the predominantly cardiac effects of these agents, except maybe in the rather rare hyperkinetic forms of hypertension.

Acute intravenous administration of beta blockers to hypertensive patients causes a significant reduction of cardiac output but no change of blood pressure due to a concomitant rise of total peripheral resistance. Long term administration of propranolol with accompanying reduction of blood pressure was initially regarded as being effective mainly through the chronic reduction of cardiac output. Later the Cleveland Clinic group has demonstrated that a gradual readjustment of total peripheral resistance down to the initial level or lower takes place during chronic treatment with propranolol, a finding confirmed by our own studies.

A reduction of plasma volume during treatment with propranolol has been reported to occur in some patients, but this finding has not been confirmed in other studies, neither as regards propranolol nor alprenolol or pindolol. It would therefore seem unlikely that the antihypertensive action of beta blockers could be attributed to a reduction of plasma volume. Even an unchanged plasma volume could be an advantage during long term therapy, however, as drug resistance due to salt and water retention, commonly seen with other agents, should not be expected to occur.

Central nervous effects. It is well known from autoradiography studies in animals that beta adrenergic blockers with few exceptions easily penetrate the blood brain barrier and are accumulated in the central nervous system. Therefore it would be conceivable that the antihypertensive effect of these agents could at least in part be explained by central nervous actions as has been suggested, e.g., by Dollery's group. On the other hand, practolol and atenolol do not penetrate the blood brain barrier and still have a clear antihypertensive action. The importance of central nervous effects is therefore uncertain at present. Further difficulties arise from studies showing alprenolol to have a central nervous action whereas propranolol does not in

Table II Hypotensive effect reported with beta adrenergic blocking drugs

Ref No	Compound	No of patients	Daily dosage (mg)	Reduction of blood pressure (mm Hg)	Remarks
16	Alprenolol	7 (15)	800	46/19	Standing BP
11	Alprenolol	41	800	14/6	
8	Propranolol	82 (1 8)	271	30/16	
10	Propranolol	232 (303)	360	57/31	+ Diuretics
19	Propranolol	20	120 240	2 /19	+ Diuretics in all + methyldopa in 4 patients
19	Alprenolol	20	300 600	20/21	
19	Pindolol	20	1 30	26/17	+ Diuretics in all + methyldopa in 4 patients
19	Timolol	20	15 30	24/14	+ Diuretics in all + methyldopa in 4 patients
17	Practolol	12 (48)	440	4?/26	+ Diuretics in ? and hydralazine in 1 patient
20	Oxprenolol	20 (31)	280	22/14	
80	Propranolol	17	320	46/25	+ Hydralazine (diuretics in patients)
62	Propranolol	11	80 240	29/24	+ Minoxidil

spite of the fact that both agents easily penetrate into the central nervous system

It is conceivable that the change of baroreceptor sensitivity that has been suggested to take place during prolonged treatment with beta blockers and which could explain the previously mentioned readjustment of total peripheral resistance may depend on central nervous actions of the drugs

Effects on the renin angiotensin system That beta adrenergic blocking agents reduce renin release and plasma renin activity in man has been demonstrated in several studies In a study that has attracted much attention Laragh's group in 1972 claimed that the antihypertensive effect of propranolol was considerably more marked in patients with high plasma renin activity in relation to their urinary sodium excretion[3] Conversely, very little effect on blood pressure was seen in the patients with low plasma renin activity Laragh and his co workers have later demonstrated the same relation between initial plasma renin activity and blood pressure response to propranolol in a study comprising a group of patients with pure essential hypertension They have also claimed that there is a significant correlation between the change of blood pressure and the change of plasma renin activity during propranolol therapy

This finding may seem appealing from a logical point of view if one regards the elevated blood pressure and the high plasma renin activity as expressions of increased sympathetic tone which are both normalized by the administration of a beta adrenergic receptor blocker There are no indications however that the renin angiotensin system has a direct influence on blood pressure in nonmalignant essential hypertension except possibly during states of severe salt depletion There is also a growing number of reports which cannot substantiate the finding that the initial plasma renin activity is of decisive importance for the antihypertensive response to beta blockade or that the change of renin is correlated to the change of blood pressure[40 44]

However recently it has been shown that low renin patients initially unresponsive to propranolol had a marked reduction of blood pressure following increased dosage This seems to indicate that both opinions in this matter may in fact be correct A number of other variables that could be expected to reflect sympathetic nervous activity e g initial heart rate cardiac output or excretion of urinary catecholamines have been shown to be of little value in predicting the antihypertensive response to beta blockade

Local anesthetic effect Studies in rabbits have indicated that the antihypertensive effect of propranolol was not related to the beta receptor blocking effect but rather to a neuron blocking

effect Clinical trials with the dextro isomer of propranolol which retains the local anesthetic effect of the racemic preparation but not the beta receptor blocking capacity have demonstrated no antihypertensive effect[4, 48] It therefore appears that the local anesthetic effect is without importance for the antihypertensive effect of beta adrenergic blocking agents in man

In summary it is difficult to provide an explanation of the antihypertensive mechanism of beta blockers that would cover all the various agents presently available Undoubtedly in most cases the effect seems to be due to a chronic reduction of cardiac output with acompanying readjustment of total peripheral resistance to the initial or a lower level It is conceivable however that an index of cardiac peformance other than cardiac output e g force of contraction (dp/dt) would be a better general denominator as the effect on cardiac output is known to be almost nonexistent with some beta blockers It is also conceivable that central nervous effects do play a role at least in modifying the hemodynamic changes The role of effects via the renin angiotensin system seems to be rather small but certainly merits further research e g along the lines of Frisk Holmberg and Shand

Selection of patients for treatment with beta blockers

It has been a common belief that patients with a hyperkinetic circulation would be particularly responsive to treatment with beta receptor blocking agents Looking solely at the antihypertensive response however such patients do not respond more favorably to treatment than others Thus no correlation can be demonstrated between initial heart rate or cardiac output and blood pressure response There is also no correlation between the change of cardiac output and the change of blood pressure during propranolol treatment Undoubtedly though there is an extra benefit of treatment with beta blockers in patients with hyperkinetic circulation as palpitations or other similar symptoms usually disappear

Another common opinion is that older patients should not be given beta blockers We do not wish to comment upon the need for antihypertensive therapy as such in the elderly[30] but beta blockers have been used successfully in the treatment of hypertensive patients over the age of 70 years[31]

Treatment with beta receptor blockers in patients with renal insufficiency has recently caused debate due to a study in which three patients with moderate renal insufficiency showed rapidly deteriorating renal function during treatment with propranolol[5] The results in these three patients are not in agreement with previous positive experience of beta blockade in uremic patients [4] Moreover it should be noted that the negative report has been refuted by the group which probably has the widest experience of treatment with beta blockers in patients with renal insufficiency

Thus it would appear that the selection of patients for antihypertensive treatment with beta blockers does not have to be limited with respect to the hemodynamic picture renal function or age of the patient We have drawn practical conclusions from this and have been using beta adrenergic blocking agents mainly propranolol and alprenolol as the first drugs of choice in the treatment of hypertension in our clinic since 1970

Contraindications and side effects

The beta adrenergic blocking agents have certain contraindications that should be strictly observed The importance of excluding patients with obstructive respiratory disease has already been touched upon at least when treatment with nonselective beta 1 and beta 2 receptor blocking agents is considered Another important (but maybe not absolute) contraindication is impending heart failure Thus in a study comprising 38 hypertensive patients with an average age of 72 years only three patients developed heart failure during alprenolol therapy two of whom could continue treatment after addition of digitalis In our own experience heart failure is extremely rare as a complication of beta adrenergic blocking therapy when treating hypertensive patients

Further contraindications are A V conduction blocks—at least A V blocks II and III—and unstable diabetes mellitus requiring insulin therapy

Early in the era of beta adrenergic blocking therapy it was already obvious that side effects were few and relatively mild Thus in a survey of 1 500 patients treated with propranolol only 98

side effects were reported, e g , vertigo fatigue, and nausea, and only 19 patients had to stop medication due to side effects [56] In a long term study comprising more than 300 hypertensive patients 67 tolerable side effects were reported and 29 patients had to be taken off the beta blocker therapy [10]

Usually side effects give subjective symptoms and they also tend to occur early during treatment This makes it possible to adjust dosage or withdraw therapy if needed during an early phase of treatment These features of beta adrenergic blocking therapy must be considered preferable to the slow onset type of metabolic disturbances without subjective symptoms that are seen with several other types of antihypertensive drugs

Beta blockers in combination with other antihypertensive agents

It has been pointed out that the combination of beta adrenergic blockade and vasodilatation offers a new aspect on the drug treatment of hypertension Several reports have also confirmed the usefulness of such combinations e g between beta blockers and hydralazine [1] or newer more potent vasodilators such as minoxidil[6] and guancydine [1] The relaxation of vascular smooth muscle with ensuing reduction of peripheral vascular resistance and blood pressure leads to a baroreceptor mediated increase of heart rate and cardiac output whereby the antihypertensive effect of the vasodilator is all but nullified Administration of a beta receptor blocker in this situation breaks this chain of compensatory mechanisms thus unmasking the full antihypertensive potential of the vasodilator, as can be clearly demonstrated in hemodynamic studies [4]

Another way of achieving peripheral vasodilatation would be to reduce vasoconstrictor activity by alpha adrenergic receptor blockade Also in this setting beta receptor blockade is desirable in order to prevent reflex induced increments of heart rate and cardiac output Initial clinical trials with combined alpha and beta receptor blockade were not successful due to the limiting side effects of alpha adrenergic blockade [65] More positive reports have been published e g on the use of oxprenolol and phentolamine [65] Our own limited experience with a new compound (AH 5158) which exhibits both alpha and beta receptor blocking capability is also quite fav r able A further way of obtaining relaxation c precapillary resistance vessels would be b specific stimulation of vascular beta 2 recept The initial clinical experience with comb beta 2 receptor stimulation and beta 1 recep blockade in hypertension has not seemed to o practical advantages, however [6]

Needless to say the combined use of a beta blocker and a diuretic also offers a useful mean by which elevated blood pressure can be reduce The combination with a diuretic is not as essen tial as e g , during treatment with sympatholytic drugs since beta blockers do not cause plasma volume expansion as discussed above An advan tage with combined beta blockade and diuretic treatment, though, would be that the doses of each drug could be reduced significantly while maintaining an adequate antihypertensive effect. This could positively affect mainly the thiazide-induced hypokalemia and hyperuricemia [6]

Additional benefits of beta receptor blockade

A number of additional benefits have been reported from the use of beta blocking therapy e g the relief of angina pectoris and migraine Of interest are also the reports on reduction of anxiety, as hypertensive patients have been reported as being more anxious than normoten sives [69] During the first years of beta blocking therapy it was reported that beta blockad reduced anxiety in neurotic patients [9] Later great interest has been focused on the effects o beta blockers in situations of stress and it ha been shown that oxprenolol given to race driver before a race will abolish the tachycardia as we as the rise of blood glucose and free fatt acids [71]

A normalization of the ECG and heart rat could also be demonstrated when a group c lecturers most of whom were physicians we given a beta blocker prior to their presenta tion [7]

In 1966 Waal[6] speculated on the possibility th beta receptor blockers given to hypertensi patients might in the long run reduce deaths fro myocardial infarction due to the antiarrhythm effect of these agents In retrospective analyses has also been shown that propranolol drasticall reduced infarct deaths in patients with know ischemic heart disease [73] Furthermore hyperte

ive patients treated with beta blockade seemed to have a three to four times lower risk of suffering a fatal infarct or sudden death [4] The reduced risk of sudden death has recently been confirmed in a prospective double blind study in which alprenolol was given to postinfarction patients Obviously these findings require further confirmation particularly as regards the beneficial effect of beta blockers in the treatment of hypertension If however it can be shown in prospective and controlled studies that deaths from ischemic heart disease can be reduced by treatment with beta blockers this would constitute a significant advantage for this type of treatment over conventional antihypertensive treatment which does not seem to reduce infarct deaths [6]

Practical considerations affecting the choice of a drug

When treating mild to moderately severe hypertension there seems to be little difference between various beta receptor blockers as regards their antihypertensive potency and side effects [15, 18, 77] In severe hypertension however beta blockers devoid of sympathomimetic properties may prove to be more effective [77]

Regarding dosage it has been claimed that an antihypertensive effect can always be expected provided that a sufficiently large dose is prescribed which has led to the administration of up to 4 Gm of propranolol a day [5] It has also been demonstrated in a small number of patients that increasing the daily dosage of propranolol also increases the antihypertensive effect [9] From a practical point of view extremely large doses of any drug are never desirable Our own policy for many years has been to use combined therapy mainly with hydralazine or diuretics if a sufficient antihypertensive effect is not seen with propranolol 300 to 600 mg daily or alprenolol 1 000 to 1 200 mg daily

When it comes to choosing between different beta receptor blockers we feel that long term experience with e g propranolol and alprenolol is such that this in itself constitutes a reason for selecting one of these older beta blockers rather than any of the more recently introduced first generation agents The situation becomes somewhat different when the new second generation beta blockers are taken into consideration e g metoprolol and atenolol as they offer certain advantages that have been discussed above The recent experience with practolol which after a few years of clinical use suddenly was found to cause serious side effects warrants carefulness and observance when newer agents are taken into use

Regarding the number of daily doses that are required in order to maintain good control of the blood pressure it is obvious that the fewer doses needed and the simpler the administration of the drug the better the patient adherance to the prescribed regimen [81] In this regard several beta blockers have been shown to maintain a stable level of blood pressure when given twice daily This is true not only of alprenolol which can be prescribed in Durules but also of propranolol [80, 8] The long duration of beta blockers as regards their effect on blood pressure can also be illustrated by the slow rise of blood pressure if treatment is stopped It has also been demonstrated that the pharmacological half life of several beta receptor blockers is considerably longer than their plasma half life [83]

Regarding onset of action it has been claimed that up to six to eight weeks of treatment would be required in order to see the full antihypertensive effect of propranolol Obviously this report of a slow onset of action could be explained by a low starting dose and a gradual buildup of dosage Our own experience indicates a much faster lowering of blood pressure during propranolol treatment [5] and in reference to pindolol it has been claimed that a significant reduction of blood pressure is seen within 20 minutes after oral administration [8]

Treatment with beta blockers and anesthesia has caused some concern The extreme opinion that beta blockers should be withdrawn 4 weeks prior to coronary bypass surgery has been based upon postoperative cardiogenic shock in five patients in a report from the Cleveland Clinic [8] Obviously one cannot exclude the possibility that the ischemic heart disease in these patients and not the treatment with a beta blocker was the main contributing factor to their myocardial failure postoperatively Our own policy regarding withdrawal or continuation of beta blocking therapy in the preoperative situation has not been uniform Undoubtedly anesthesia can be performed in most cases without previous with

drawal of beta blocking treatment If, however discontinuation of therapy is desired, we have usually done so 2 days preoperatively This will not bring blood pressure back to the untreated level in most patients as has already been discussed, but resting heart rate will rise to the initial level (or higher), indicating that beta blockade is not present

Future lines of development

Future development of antihypertensive therapy can be expected to follow three main lines A further refinement of central nervous system-acting drugs of the clonidine type can be expected leading to drugs that give less sedation A second possible line of development would be the production of more potent vasodilators, and some of these, e g, minoxidil and guancydine have already been touched upon here However, with more potent vasodilators it will become mandatory to administer both a beta blocker and a diuretic to prevent reflex tachycardia and fluid retention Thus the vasodilators cannot be expected to serve as the first drugs of choice as they should be reserved for cases needing multiple drug therapy

Finally a refinement of the beta receptor blockers can be foreseen and some of the second generation beta blockers already look promising as regards their antihypertensive effect Thus atenolol[illegible] and metoprolol[illegible] have been shown to have a useful blood pressure-lowering effect and comparatively few and mild side effects The advantage of selective beta 1 receptor blockade is that bronchial beta 2 receptors are not blocked thereby reducing the risk of bronchoconstriction It is also conceivable that the unblocked vascular beta 2 receptors may contribute to less pronounced rises of blood pressure during episodes of increased release of catecholamines e g during mental stress or physical exercise Furthermore the lack of a sympathomimetic effect with both atenolol and metoprolol could be an advantage at least when treating severe hypertension

Seen against this background it is possible that future treatment of hypertension will be even more dependent upon drugs with a beta receptor blocking activity than is the case today We wish to stress once again though that the positive experience with some of the newer agents should be confirmed in larger series with long periods of follow up before one can state that these agents are as safe as "first generation" beta blockers

REFERENCES

1 Schroder G and Werko L Nethalide a beta adrenergic blocking agent Clin Pharmacol Ther 5 159 1964
2 Prichard B N C and Gillam P M S The use of propranolol in the treatment of hypertension Br Med J 2 725 1964
3 Paterson J W and Dollery C T Effect of propranolol in mild hypertension Lancet 2 1148 1966
4 Prichard B N C and Gillam P M S Propranolol in hypertension Am J Cardiol 18 387 1966
5 Prichard B N C and Gillam P M S Treatment of hypertension with propranolol Br Med J 1 7 1969
6 Waal H J Hypertensive action of propranolol Clin Pharmacol Ther 7 588 1966
7 Frohlich E D Tarazi R C Dustan H P and Page I H The paradox of beta adrenergic blockade in hypertension Circulation 37 417 1968
8 Hansson L Malmcrona R Olander R Rosenhall, L, Westerlund A Aberg H and Hood B Propranolol in hypertension Report on 158 patients treated up to one year Klin Wochenschr 50 364 1972
9 Karlberg B and Hornkvist P E Propranolol in treatment of hypertension Opusc Med 6 296 1971
10 Zacharias F J Cowen K J Prestt J Vickers J and Wall B G Propranolol in hypertension A study of long term therapy 1964 1970 Am Heart J 83 755 1972
11 Lydtin H Kusus T Daniel W Schierl W Ackenheil, M Kempter H Lohmöller G Niklas M and Walter I Propranolol therapy in essential hypertension Am Heart J 83 589 1972
12 Furberg C and Michaelson G Effect of Aptin a beta adrenergic blocking agent in arterial hypertension Acta Med Scand 186 447 1968
13 Tibblin C and Åblad B Antihypertensive therapy with alprenolol a beta adrenergic antagonist Acta Med Scand 186 451 1968
14 Bengtsson C Comparison between alprenolol and chlorthalidone as antihypertensive agents Acta Med Scand 191 433 1972
15 Bengtsson C Comparison between alprenolol and propranolol as antihypertensive agents Acta Med Scand 192 415 1972
16 Vedin A Wilhelmsson C and Werkö L Comparative study of alprenolol and methyldopa in previously untreated essential hypertension Br Heart J 35 1285 1973
17 Prichard B N C Boakes A J and Day G Practolol in the therapy of hypertension Postgrad Med J 47 (Suppl) 84 1971
18 Andersson O and Berglund G Practolol propranolol Comparison of the antihypertensive effect Acta Med Scand 1974
19 Morgan T O Sabro J Anavekar S N Louis W J and Doyle A E A comparison of beta adrenergic blocking drugs in the treatment of hypertension Postgrad Med J 50 253 1974
20 Dorph S and Binder C Evaluation of the hypotensive effect of beta adrenergic blockade in hypertension Acta Med Scand 185 443 1968
21 Coltart D J Assessment of beta adrenergic blocking

and non specific properties of propranolol Br Heart J 30 615 1971
22 Freis E D Hemodynamics in hypertension Physiol Rev 40 27 1960
23 Ulrych, M Frohlich E D Dustan H P and Page I H Immediate hemodynamic effects of beta adrenergic blockade with propranolol in normotensive and hypertensive man Circulation 37 411 1968
24 Hansson L Zweifler A J Julius S and Hunyor S N Hemodynamic effects of acute and prolonged beta adrenergic blockade in essential hypertension Acta Med Scand 196 27 1974
25 Tarazi R C and Dustan H P Beta adrenergic blockade in hypertension Practical and theoretical implications of long term hemodynamic variations Am J Cardiol 29 633 1972
26 Tarazi, R C Frohlich E D and Dustan, H P Plasma volume changes and beta adrenergic blockade Am Heart J 82 770 1971
27 Sederberg Olsen P and Ibsen H Plasma volume and extracellular fluid volume during long term treatment with propranolol in essential hypertension Clin Sci 43 165 1972
28 Mosbaek N Effekt af alprenolol pa plasmavolumen ekstracellular volumen og den glomerulare filtration *in* Ibsen H editor Symposium om Hypertension og Beta receptor Blokade Kopenhamn 19 4 ICI Pharma AS p 15
29 Parving H Effekt av pindolol pa plasmavolumen og den transkapillare escape rate af 131 I albumin *in* Ibsen H editor Symposium on Hypertension og Beta receptor Blokade Kopenhamn 1974 ICI Pharma AS p 19
30 Finnerty F Relationship of extracellular fluid volume to the development of drug resistance in the hypertensive patient Am Heart J 81 563 1971
31 Dollery C T Lewis P J Myers M G and Reid J L Central hypotensive action of propranolol in the rabbit Br J Pharmacol 48 343P 1973
32 Lewis, P J Myers M G Reid J L and Dollery C T Mechanism of beta blockade hypotension N Engl J Med 288 689 1973
33 Hansson L Aberg H Jameson S Karlberg B and Malmcrona R Initial clinical experience with ICI 66 082 a new beta adrenergic blocking agent in hypertension Acta Med Scand 195 549 1973
34 Offerhaus L and van Zweiten P A Comparative studies on central factors contributing to the hypotensive action of propranolol alprenolol and their enantiomers Cardiovasc Res 8 488 1974
35 Hansson L Beta adrenergic blockade in essential hypertension Effects of propranolol on hemodynamic parameters and plasma renin activity Acta Med Scand 550(Suppl) 1 1973
36 Winer N Chokshi, D S Yoon M S and Freedman A D Adrenergic receptor mediation of renin release J Clin Endocrinol Metab 29 1168 1968
37 Michelakis, A M and McAllister R G The effect of chronic adrenergic receptor blockade on plasma renin activity in man J Clin Endocrinol Metab 34 386 1972
38 Buhler F R Laragh J H Baer L Vaughan E D and Brunner H R Propranolol inhibition of renin secretion, N Engl J Med 287 1209 1972
39 Buhler F R, Laragh, J H Vaughan E D Jr Brunner H R Gavras, H and Baer L Antihypertensive action of propranolol Am J Cardiol 32 511 1973
40 Birkenhäger W H Krauss X H Schalekamp,M A D H Kolsters, G and Kroon B U M Antihypertensive effects of propranolol Observations on predictability Folia Med Neerl 14 67 1971
41 George C F Round table on renin suppression and the hypotensive effect of beta adrenergic blocking agents, *in* Third meeting of the International Society of Hypertension Milano 1974 Clin Sci Mol Med 48(Suppl 2) 1975
42 Hansson L and Zweifler A J The effect of propranolol on plasma renin activity and blood pressure in mild essential hypertension Acta Med Scand 195 397 1974
43 Morgan T O Round table on renin suppression and the hypotensive effect of beta adrenergic blocking agents *in* Third meeting of the International Society of Hypertension Milano 1974 Clin Sci Mol Med 48(Suppl 2) 1975
44 Stokes G S Weber M A and Thornell I R Beta blockers and plasma renin activity in hypertension Br Med J 1 60 1974
45 Hansson L Zweifler A J Julius S and Ellis C N Propranolol therapy in essential hypertension Observations on predictability of therapeutic response Int J Clin Pharmacol 10 79 1974
46 Eliash S and Weinstock M Role of adrenergic neurone blockade in the hypotensive action of propranolol, Br J Pharmacol 43 287 1971
47 Waal Manning H J Lack of effect of d propranolol on blood pressure and pulse rate in hypertensive patients Proc Univ Otago Med School 48 80 1970
48 Rahn K Hawlina A Kersting F and Planz G Studies on the antihypertensive action of the optical isomers of propranolol in man Naunyn Schmiedeberg Arch Pharmacol 286 319 1974
49 Frisk Holmberg M and Shand D G A dual antihypertensive mechanism for propranolol *in* Berglund G Hansson L and Werko L editors The pathophysiology and management of arterial hypertension Astra Int Ltd Copenhagen 1975
50 Fry J Natural history of hypertension Lancet 2 431 1974
51 Eisalo A, and Munter J The effect of alprenolol in elderly patients with raised blood pressure Acta Med Scand 554(Suppl) 23 1974
52 Warren D J Swainson C P, and Wright N Deterioration in renal function after beta blockade in patients with chronic renal failure and hypertension Br Med J 2 193 1974
53 *Jameson S Effekten av Inderal* vid behandling av uremisk hypertension Nord Med 44 1282 1971
54 Franzén P and Pasternack A Propranolol in renal failure Br Med J 2 763 1972
55 Kincaid Smith, P and Hua A S P Beta adrenergic blocking agents in renal failure Br Med J 3 520 1974
56 Stephen S A Unwanted effects of propranolol Am J Cardiol 18 463 1966
57 Werkö L New treatment for hypertension Eur J Clin Pharmacol 3 61 1971
58 Hansson L Olander R Malmcrona R and Westerlund A Treatment of hypertension with propranolol and hydralazine Acta Med Scand 190 531 1971
59 Gottlieb T B Katz F H and Chidsey C A Combined therapy with vasodilator drugs and beta adrenergic blockade in hypertension Circulation 45 571 1972
60 Hansson L and Zweifler A J Combined treatment of hypertension with vasodilation and beta adrenergic blockade Mich Med 72 795 1973

61 Katıla M and Frick M H Combined dihydralazine and propranolol in the treatment of hypertension Int J Clin Pharmacol **4** 111 1970

62 Gilmore E Weil J and Chidsey C Treatment of essential hypertension with a new vasodilator in combination with beta adrenergic blockade N Engl J Med **282** 521 1970

63 Hansson L Vedin A Werkö L and Wilhelmsson C Controlled study of guancydine in hypertension 1974

64 Sannerstedt R Stenberg J Johnsson G and Werko L Hemodynamic interference of alprenolol with dihydralazine in normal and hypertensive man Am J Cardiol **28** 316 1971

65 Beilin L J and Juel-Jensen B F Alpha and beta adrenergic blockade in hypertension Lancet **1** 979 1972

66 Majid P A Meeran M K Benaim M E Sharma B and Taylor S H Alpha and beta adrenergic receptor blockade in the treatment of hypertension Br Heart J **36** 588 1974

67 Andersson O and Berglund G Combined therapy with beta 2 receptor stimulation and beta 1 receptor blockade in hypertension Acta Med Scand **197** 495 1975

68 Angervall G and Bystedt U The effect of alprenolol in combination with saluretics in hypertension Acta Med Scand **554**(Suppl) 39 1974

69 Wheatly D Psychiatric aspects of hypertension Psychopharmacol Bull **10** 4 1974

70 Granville Grossman K L and Turner P The effect of propranolol on anxiety Lancet **1** 788 1966

71 Taggart P and Carruthers S M Suppression by oxprenolol of adrenergic response to stress Lancet **2** 256 1972

72 Taggart P Carruthers S M and Somerville W Electrocardiogram plasma catecholamines and lipids and their modification by oxprenolol when speaking before an audience Lancet **2** 341 1973

73 Lambert D M D Beta blockers and life expectancy in ischemic heart disease Lancet **1** 793 1972

74 Lambert D M D Hypertension and myocardial infarction Lancet **2** 685 1974

75 Wilhelmsson C Vedin A Wilhelmsen L Tibblin G and Werko L Reduction of sudden deaths after myocardial infarction by treatment with alprenolol Lancet **2** 1157 1974

76 Veterans Administration Co operative Study Group on Antihypertensive Agents Effects of treatment on morbidity in hypertension J A M A **213** 1143 1970

77 Kincaid Smith P Management of severe hypertension Am J Cardiol **32** 575 1973

78 Berglund G and Hansson L A within patient comparison of alprenolol and propranolol in hypertension Acta Med Scand **193** 547 1973

79 Kincaid Smith P Fang P and Laver M A new look at the treatment of severe hypertension Clin Sci Mol Med **45**(Suppl 1) 75P 1973

80 Hansson L Olander R and Aberg H Twice-daily propranolol treatment for hypertension Lancet **2** 11 1971

81 Malahy B The effect of instruction and labelling on the number of medication errors made by patients at home Am J Hosp Pharm **23** 283 1966

82 Berglund G Andersson O Hansson L and Olander R Propranolol given twice daily in hypertension Acta Med Scand **194** 513 1973

83 Carruthers S G Kelly J G McDevitt D G Shanks R G and Walsh M J Duration of action of beta blocking drugs Br Med J **2** 177 1973

84 Doyle A E in Berglund G Hansson L and Werkö L editors The pathophysiology and management of arterial hypertension Copenhagen 1975 A[illegible] Ltd

85 Viljoen J F Estafanous F G and Kellner G A Propranolol and cardiac surgery *J Thorac Cardiovasc Surg* **64** 826 1972

86 Amery A Billiet L Joosens J V Meekers J Reybrouckt T and van Mieghem W Preliminary report on the haemodynamic response of hypertensive patients treated with a beta blocker (ICI 66 082) Acta Clin Belg **28** 358 1973

87 Hansson L Henningsen N C Karlberg B E Aberg H Jameson S Malmcrona R and Hersvall C Hypotensive action of ICI 66 082 a new beta adrenergic blocking agent Int J Clin Pharmacol **10** 206 1974

88 Hansson L Aberg H Karlberg B E and Westerlund A Controlled study of Tenormin (ICI 66 082) in the treatment of hypertension Br Med J **2** 367 1975

89 Bengtsson C The effect of the cardioselective beta blocker metoprolol in essential hypertension 1974 (To be published)

90 Berglund G Bergstrand R Vedin A and Wilhelmsson C A comparative study of the efficacy of the cardioselective beta blocker metoprolol and alphamethyldopa in previously untreated patients with essential hypertension 1974 (To be published)

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Ventricular unloading in the management of heart disease Role of vasodilators Part II

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Sodium nitroprusside (continued)

Valvular heart disease

Mitral regurgitation Nitroprusside has been used successfully to produce symptomatic and objective improvement in valvular subvalvular and periprosthetic mitral regurgitation [3] A reduction in left atrial or wedge V wave and mean pulmonary wedge pressures are associated with increases in forward stroke volume and decreases in regurgitant fraction

Nitroprusside may allow stabilization and post ponement of definitive surgery in seriously ill patients with acute and/or severe mitral insufficiency to a later and safer date

Aortic regurgitation Clinical improvement with reduced regurgitant fraction end diastolic volume and pressure and increased forward stroke volume has been demonstrated in both chronic and acute aortic insufficiency [5] Furthermore nitroprusside abolishes the premature mitral valve closure caused by the abnormal reversal of the left ventricular to left atrial end diastolic gradient in severe aortic insufficiency [6] A possible limitation to the use of the drug in aortic insufficiency would appear to be the deleterious effects of a decrease in the already low coronary perfusion pressure (aortic diastolic pressure)

Mitral stenosis Afterload reduction with nitroprusside in most patients with mitral stenosis is of little benefit as it is not associated with an increase in cardiac output Markedly elevated pulmonary artery pressure may be significantly decreased It is probable that in hypertensive patients with mitral stenosis nitroprusside therapy may be helpful since angiotensin induced elevation of afterload in patients with mitral stenosis causes increase in pulmonary wedge pressure and a decrease in cardiac output [7]

Miscellaneous

Post infarction VSD This complication of acute myocardial infarction is associated with a high (70 to 80 per cent) mortality rate whether approached medically or with corrective surgery Nitroprusside may decrease the degree of left to right shunt and improve ventricular function allowing postponement of corrective surgery to a later and safer date Personal experience with four such cases however has not been encouraging

Cardiac surgery In patients with depressed ventricular function during coronary artery bypass surgery nitroprusside can improve ventricular function [8] In the immediate postoperative period afterload reduction with nitroprusside in cardiac surgical patients has been associated with an increase in cardiac output [9] More studies need be done to confirm its beneficial effects in the management of post surgical low output states

Advantages of nitroprusside over other parenteral vasodilators Very few comparative studies of nitroprusside and other vasodilators have been done From the available data it appears that nitroprusside generally does not demonstrate tachyphylaxis and does not have the disturbing ganglioplegic side effects of trimethaphan Nitroprusside seldom causes the tachycardia which is seen with phentolamine Intravenous nitroglycerin appears to have predominantly a preload reducing effect thereby decreasing left ventricular filling pressure often without change[10, 11] or with an actual decrease in stroke volume [8] Nitroprusside on the other hand appears to have a

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relatively more balanced effect on preload and afterload thereby improving stroke volume concomitant with a reduction in left ventricular filling pressure

Toxicity The most dangerous complication of nitroprusside therapy is precipitous hypotension with its deleterious consequences This effect is rapidly reversed on cessation or decrease in infusion rate Rarely, more prolonged and unexpected hypotension may occur during its use Nausea and vomiting may occur early in the course of therapy Prolonged and high dose infusions, especially in patients with renal failure, may result in thiocyanate accumulation with development of reversible hypothyroidism[11,12] Headache flushing, anorexia, mental aberration, muscle spasms and skin rash may also occur during its use An angina line syndrome in a child was produced and attributed to interference with oxygen utilization produced by cyanogen[13] Effect of hepatic disease on nitroprusside toxicity has not been studied Methemoglobinemia from prolonged use has also been reported

Precautions Nitroprusside should be freshly prepared every four hours and infused through a free flowing intravenous line which is protected from light A low flow constant infusion pump for precise tailoring of the dose is strongly recommended Frequent measurements of cardiac output intra arterial blood pressure and pulmonary artery pressure monitoring (with Swan Ganz catheter) are strongly advised to prevent precipitous hemodynamic changes and to guide and titrate the dosage to achieve the lowest left ventricular filling pressure with maximum stroke volume and minimum hypotension and tachycardia

The dosage may range from 10 to 800 μg/min and should be increased step wise every 5 to 10 minutes beginning with 10 to 20 μg/min until an optimum hemodynamic effect is produced Although the dose requirement remains within a fairly narrow range once the effective level is achieved, occasionally increasing drug infusion rates are needed to produce a similar hemodynamic response Possible mechanisms for this observation include too much volume administration of the vehicle for nitroprusside, secondary hyperaldosteronism which may occur due to increase in plasma renin activity[14] The latter may also explain continued need for diuretics, albeit at lower doses in some patients to maintain adequate urine output in spite of a substantial improvement in cardiac output To avoid bolus injections of nitroprusside the infusion line should not be flushed without first clearing the intravenous tubing of residual nitroprusside For the same reason, no other medication should be given through the nitroprusside line Sudden cessation of nitroprusside infusion may cause rapid and severe symptomatic and hemodynamic rebound This is more likely to occur in patients who show substantial improvement on nitroprusside Therefore, withdrawal from nitroprusside should be gradual in such patients (unpublished observations) Serum thiocyanate levels during large dose or prolonged infusion should be measured to avoid levels in excess of 10 mg/100 ml

Non parenteral vasodilators

Symptomatic and hemodynamic improvement with rapidly acting parenteral vasodilators in congestive heart failure and low cardiac output states has been well established but their usefulness is seriously limited by the need for meticulous invasive monitoring thus these agents are unsuitable for long term management Therefore the use of non parenteral vasodilators, chiefly nitrates as impedance lowering agents has been investigated

Nitrates in congestive heart failure In addition to the predominantly venodilator and hence preload reducing effect nitrates have a variable arteriolar dilatory (afterload reducing) effect[15] They may also cause redistribution of regional myocardial blood flow,[16] increase coronary collateral blood flow and have salutary electrophysiologic effects[17]

Chief drawbacks of their use include unpredictable hypotension which may be orthostatic, reflex tachycardia, flushing and headache, methemoglobinemia, occasionally tachyphylaxis, and a potential increase in myocardial ischemia created by a coronary steal effect[18] A predominant preload reducing effect with a variable decrease in afterload may account for variable effects on stroke volume even though left ventricular filling pressures are usually decreased

Four non parenteral forms of nitrates have been used for congestive heart failure

Sublingual Nitroglycerin in doses of 0 4 to 0 6

mg reduces left ventricular filling pressure with variable effects on stroke volume within 3 to 5 minutes and peak effects are observed at 15 to 20 minutes However the short duration of effect which seldom lasts more than 30 minutes and the variable and possible deleterious effects on stroke volume limit its usefulness [3]

Sublingual isosorbide dinitrate This agent in doses of 5 to 20 mg also reduces left ventricular filling pressures within 15 minutes with peak effects observed at 15 to 45 minutes The effect generally lasts two hours or less although in one study hemodynamic effects were observed to last as long as four hours [5] The effect on stroke volume varies from no increase to a modest rise These effects have been observed during acute myocardial infarction as well as in chronic congestive heart failure Isosorbide dinitrate has not been observed to worsen ischemia as measured by myocardial lactate production or arterial coronary sinus oxygen difference

Chewable isosorbide dinitrate A limited study using 10 mg of this agent has shown that it also lowers left ventricular filling pressure within five minutes to peak effects noted at 15 minutes The duration of effect is approximately three hours Cardiac output is generally increased If these results are confirmed then this agent may serve as a reasonable choice for long term therapy

Oral isosorbide dinitrate Considerable doubt about the effectiveness of oral isosorbide dinitrate has been raised by experiments showing minimal plasma levels of unaltered drug after its oral or intraportal administration in rats This was attributed to hepatic enzymatic biotransformation Such enzymes are present in abundance in the human liver Although high levels of its metabolites in blood can be detected in dogs after oral administration pharmacological activity of such agents has not been established However in a small number of patients oral isosorbide dinitrate in doses of 20 mg has caused a significant reduction in left ventricular filling pressure lasting 4½ to 6 hours without a change in cardiac output [78]

Topical nitroglycerin Preliminary data show that 2 per cent nitroglycerin in an ointment base applied cutaneously under an occlusive dressing is effective in lowering both left ventricular filling pressure and the magnitude of V waves in mitral regurgitation [10] It may also increase stroke volume in some patients The effects may last from three to six hours and the dosage and surface area of application can be varied depending upon the desired hemodynamic effects

Other non parenteral agents Other non parenteral agents that have been studied on a limited basis include the α adrenergic blocking agent phenoxybenzamine and direct arteriolar dilating agent hydralazine [3] Further studies with these agents must be done to confirm preliminary reports and establish their role for chronic impedance reduction therapy

Conclusion

Use of vasodilators seem to be effective in symptomatic management of many patients with severe or refractory pump failure with or without valvular regurgitation However a search for safe effective and long acting non parenteral agents should continue in order to make long term impedance reduction therapy practical

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REFERENCES

1 Harshaw C W Grossman W et al Reduced systemic vascular resistance as therapy for severe mitral regurgitation of valvular origin Ann Intern Med **83** 312 1975
2 Chatterjee K Parmley W W Swan H J C et al. Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvular apparatus Circulation **48** 684 1973
3 Goodman D J Rossen R M Holloway E L et al. Effects of nitroprusside on left ventricular dynamics in mitral regurgitation Circulation **50** 1025 1974
4 Miller R R Vismara L A Williams D O et al Effects of ventricular unloading with nitroprusside in severe aortic regurgitation reduced regurgitant volume and improved cardiac performance Am J Cardiol **37** 156 1976
5 Bolen J L and Alderman E L. Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation Circulation **53** 879 1976
6 Pepine C J Nichols W W., Curry R C and Conti C R Reversal of premature mitral valve closure by nitroprusside infusion in severe aortic insufficiency Am J Cardiol **37** 161 1976
7 Bolen, J L Lopes M G et al Analysis of left ventricular function in response to afterload changes in patients with mitral stenosis Circulation **52** 894 1975
8 Lappas, D G Waller J L Lowenstein E et al. Intraoperative effects of *nitroprusside* in patients with coronary artery disease Circulation **51** (Suppl II) II 119 1975
9 Stinson E B Holloway E L Griepp R B et al Comparative hemodynamic responses to chlorpromazine nitroprusside and nitroglycerin immediately after

open heart operations Circulation (Suppl III) III 19 1974
10 Armstrong P Walker D Benton J R et al Vasodilator therapy in acute myocardial infarction Circulation **52** 1118 1975
11 Flaherty J T Reid P R Kelly D T et al Intravenous nitroglycerin in acute myocardial infarction Circulation **51** 132 1975
12 Nourok D S Glassock R J Solomon D H et al Hypothyroidism following prolonged sodium nitroprusside therapy Am J Med Sci **248** 129 1964
13 Palmer R F and Lasseter K C Sodium nitroprusside N Engl J Med **292** 294 1975
14 Kaneko Y Ikeda T Takeda T et al Renin release during acute reduction of arterial pressure in normal subjects and patients with renovascular hypertension J Clin Invest **46** 705 1967
15 Mason D T and Braunwald E The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm Circulation **32** 755 1965
16 Kent K M Smith E R Redwood D R and Epstein S E Beneficial electrophysiologic effects of nitroglycerin during acute myocardial infarction Am J Cardiol **33** 513 1974
17 Winbury M M Howe V V and Weiss H R Effect of nitroglycerin and dipyridamole on epicardial and endocardial oxygen tension—further evidence for redistribution of myocardial blood flow J Pharmacol Exp Ther **176** 84 1971
18 Forman R Kirk F S Downey J M et al Nitroglycerin and heterogeneity of myocardial blood flow Reduced subendocardial blood flow and ventricular contractile force J Clin Invest **52** 905 1973
19 Mikulic E Franciosa J A and Cohn J N Comparative hemodynamic effects of chewable isosorbide dinitrate and nitroglycerin in patients with congestive heart failure Circulation **52** 477 1975
20 Korick R Tillish J H et al Vasodilator therapy for chronic left ventricular failure Circulation **53** 322 1976
21 Gold H K Leinbach R L and Sanders C A Use of sublingual nitroglycerin in congestive failure following acute myocardial infarction Circulation **46** 839 1972
22 Mikulic E Franciosa J A and Cohn J N Comparative hemodynamic effects of nitroglycerin forms in heart failure Circulation **51** (Suppl II) II-36 19 5
23 Williams D O Amsterdam F A and Mason D T Hemodynamic effects of nitroglycerin in acute myocardial infarction Decrease in ventricular preload at the expense of cardiac output Circulation **51** 421 1975
24 Gray R Chatterjee K Vyden J K et al Hemodynamic and metabolic effects of isosorbide dinitrate in chronic congestive heart failure AM HEART J 90 346 1975
25 Mantle J A Russel R O Moraski R and Rackley C E Isosorbide dinitrate for the relief of severe heart failure after myocardial infarction Am J Cardiol **37** 263 1976
26 Needleman P Lang S and Johnson E M Organic nitrates relationship between biotransformation and rational angina pectoris therapy J Pharmacol Exp Ther **181** 489 1972
27 Sisenwine S F and Ruelius, H W Plasma concentrations and urinary excretion of isosorbide dinitrate and its metabolites in the dog J Pharmacol Exp Ther **176** 296 1971
28 Williams D O Bonimer W Merwin R et al Prolonged effectiveness of oral vasodilator therapy in chronic congestive heart failure with isosorbide dinitrate Am J Cardiol **37** 182 1976
29 Franciosa J A Mikulic E Cohn J N et al Hemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure Circulation **50** 1020 1974
30 Taylor W R Forrester J S Magnusson P et al The hemodynamic effects of nitroglycerin ointment in congestive heart failure Circulation **51** (Suppl. II) II-36 1975
31 Meister S F Furr C Feitosa G et al Sustained hemodynamic effects of nitroglycerin ointment Am J Cardiol **37** 155 1976
32 Franciosa J and Cohn J N Hemodynamic improvement with hydralazine in left heart failure Clin Res **24** 217 1976

The remote prognosis of eclamptic women

A continuing follow up study of women surviving eclampsia at the Margaret Hague Maternity Hospital in Jersey City N J was begun in 193 From the opening of the hospital in 1931 through 1951 *there were 270 survivors* all but three of whom *were traced to 19 3-74*

A comparison of women who had eclampsia in the first pregnancy carried to viability (primiparas) with those having had eclampsia in later pregnancies ("multiparas) shows greatly different prognoses The 31 remote deaths among the 18 white primiparas who constitute 0 per cent of the series does not differ significantly from the number to be expected in unselected women matched for age and race Only 29 per cent of the remote deaths were from cardiovascular disease and the prevalence of hypertension at an average of 33 years after eclampsia is not increased over that to be expected on the basis of age-specific prevalences provided in several *epidemiologic studies* Nearly 90 per cent of the women still living are now aged 50 years or more and few now normotensive are likely to develop essential hypertension Therefore eclampsia is not merely a sign of latent essential hypertension brought to light and peculiarly colored by pregnancy as some ... believed in the past Neither does prolonged preeclampsia–eclampsia cause chronic hypertension in women who otherwise would never have developed it

In striking contrast 33 of 59 white multiparas (56 per cent) have died and that is ? 75 times the expected number Eighty two per cent of the remote deaths have been caused by cardiovascular disease and there is an excess of observed over the expected number with hypertension Chronic hypertension antedated the eclamptic pregnancy in about half of the multiparas and predisposed them to eclampsia in the first place The antecedent hypertension was documented in some cases and in others it was inferred from such signs as retinal angiosclerosis cardiac enlargement *exorbitant hypertension* during eclampsia and earlier hypertensive pregnancies

The prevalencies of diastolic pressures of 100 mm Hg or higher are ?8 per cent among the primiparas having had no later viable pregnancy and 2? per cent among the 151 who have had later viable gestations Later pregnancies *therefore* have not caused hypertension even though one third of the women had hypertension during the later pregnancies Among the 100 whose later gestations were normotensive the prevalence of diastolic pressures of 100 mm Hg or higher is 10 per cent as compared with 45 per cent in the 51 who have had at least one later hypertensive pregnancy It appears that the later gestations have served as a screening test for ultimate essential hypertension Women who have the hypertensive diathesis manifest it by gestational hypertension whereas those who will remain normotensive have normotensive pregnancies.

The prevalence of diabetes of late onset is ?5 times the expected in the primiparas and about 4 times the expected in multiparas

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REFERENCE

1 Chesley L. C Annitto J E., and Cosgrove R A The remote prognosis of eclamptic women sixth periodic report Am J Obstet Gynecol. 124 446 1976

Atenolol in hypertension

Atenolol (ICI 66082 Tenormin) is a new cardioselective adrenoceptor beta blocking agent of similar potency to propranolol in animals that lacks significant partial agonist and membrane stabilizing activity The formulae of atenolol (4 (2 hydroxy 3-isopropylamino propoxy]phenylacetamide) and the cardioselective beta blocker practolol (4 [2 hydroxy 3-isopropylamino-propoxy]acetanilide) look similar but differ chemically in the side chains and in their theoretical metabolites Now that oral practolol has been withdrawn because of the association with an oculomucocutaneous syndrome there is a need for effective and safe oral cardioselective beta blockers

Dollery Lewis, and Myers have reported a clinical evaluation of atenolol. Patients who had received no antihypertensive therapy for at least *two weeks were started* on a dose of 75 mg /day and the dose increased at *two-weekly intervals* to a maximum of 900 mg /day On the maximum effective dose (mean 337.5 mg /day) *a fall in* supine and erect blood pressures of 28/18 and 35/15 mm. Hg was observed from a starting level after a *run in period of 187/114* and 187/115 mm Hg respectively The plotted dose response curve was flat with *daily doses of 75 150 300* and 600 mg producing similar reductions in blood pressure When the maximum effective *dose had been determined* each patient was randomly allocated into a double blind cross-over study comparing atenolol with *placebo Arterial* pressure and heart rate were signifi

open heart operations Circulation (Suppl III) III 19 1974
10 Armstrong P Walker D Benton J R et al Vasodilator therapy in acute myocardial infarction Circulation 52 1118 1975
11 Flaherty J T Reid P R Kelly D T et al Intravenous nitroglycerin in acute myocardial infarction Circulation 51 132 1975
12 Nourok D S Glassock R J Solomon D H et al Hypothyroidism following prolonged sodium nitroprusside therapy Am J Med Sci 248 129 1964
13 Palmer R F and Lasseter K C Sodium nitroprusside N Engl J Med 292 294 1975
14 Kaneko Y Ikeda T Takeda T et al Renin release during acute reduction of arterial pressure in normal subjects and patients with renovascular hypertension J Clin Invest 46 705 1967
15 Mason D T and Braunwald E The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm Circulation 32 755 1965
16 Kent K M Smith E R Redwood D R and Epstein S E Beneficial electrophysiologic effects of nitroglycerin during acute myocardial infarction Am J Cardiol 33 513 1974
17 Winbury M M Howe V V and Weiss H R Effect of nitroglycerin and dipyridamole on epicardial and endocardial oxygen tension—further evidence for redistribution of myocardial blood flow J Pharmacol Exp Ther 176 84 1971
18 Forman R Kirk E S Downey J M et al Nitroglycerin and heterogeneity of myocardial blood flow Reduced subendocardial blood flow and ventricular contractile force J Clin Invest 52 905 1973
19 Mikulic E Franciosa J A and Cohn J N Comparative hemodynamic effects of chewable isosorbide dinitrate and nitroglycerin in patients with congestive heart failure Circulation 52 477 1975
20 Korick R Tillish J H et al Vasodilator therapy for chronic left ventricular failure Circulation 53 322 1976
21 Gold H K Leinbach R L and Sanders C A Use of sublingual nitroglycerin in congestive failure following acute myocardial infarction Circulation 46 839 1972
22 Mikulic E Franciosa J A and Cohn J N Comparative hemodynamic effects of nitroglycerin forms in heart failure Circulation 51 (Suppl II) II 36 19 5
23 Williams D O Amsterdam E A and Mason D T Hemodynamic effects of nitroglycerin in acute myocardial infarction Decrease in ventricular preload at the expense of cardiac output Circulation 51 421 1975
24 Gray R Chatterjee K Vyden J K et al Hemodynamic and metabolic effects of isosorbide dinitrate in chronic congestive heart failure Am Heart J 90 346 1975
25 Mantle J A Russel R O Moraski R and Rackley C E Isosorbide dinitrate for the relief of severe heart failure after myocardial infarction Am J Cardiol 37 263 1976
26 Needleman P Lang S and Johnson E M Organic nitrates relationship between biotransformation and rational angina pectoris therapy J Pharmacol Exp Ther 181 489 1972
27 Sisenwine S F and Ruelius H W Plasma concentrations and urinary excretion of isosorbide dinitrate and its metabolites in the dog J Pharmacol Exp Ther 176 296 1971
28 Williams D O Bonimer W Merwin R et al Prolonged effectiveness of oral vasodilator therapy in chronic congestive heart failure with isosorbide dinitrate Am J Cardiol 37 182 1976
29 Franciosa J A Mikulic E Cohn J N et al Hemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure Circulation 50 1020 1974
30 Taylor W R Forrester J S Magnusson P et al The hemodynamic effects of nitroglycerin ointment in congestive heart failure Circulation 51 (Suppl II) II-35 1975
31 Meister S F Furr C Feitosa G et al Sustained hemodynamic effects of nitroglycerin ointment Am J Cardiol 37 155 1976
32 Franciosa J and Cohn J N Hemodynamic improvement with hydralazine in left heart failure Clin Res 24 217 1976

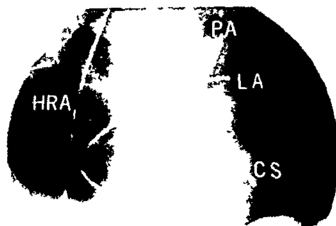


Fig 1 Roentgenogram showing the catheter positions from which the different atrial electrograms were obtained *HRA* = high right atrium *LA* = left lateral atrium *CS* = distal coronary sinus *PA* = main pulmonary trunk.

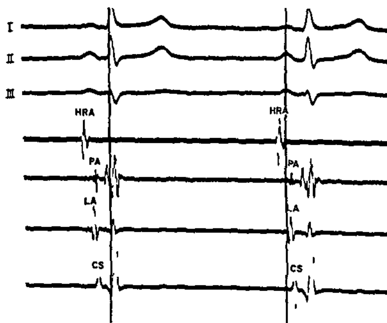


Fig 2 Shown are electrocardiographic Leads I II and III *HRA* = high right atrial electrogram *PA* = left anterior atrial electrogram *LA* = left lateral atrial electrogram *CS* = left posterior electrogram from coronary sinus. Time lines are at 100 mm /sec See text for discussion

electrogram corresponds to local activation of the left atrial appendage (anterior left atrium) which anatomically is in close proximity to the pulmonary trunk Fig 2 is a representative example Simultaneous recordings were obtained in a patient in which catheters were placed in the high right atrium (HRA) lateral left atrium (LA) via a patent foramen ovale distal coronary sinus (CS) and main pulmonary trunk (PA)

Note that the local electrogram from PA is inscribed 80 msec after HRA activation at the end of the P wave following left lateral atrial activation and preceding the posterior left atrial electrogram (CS) A ventricular electrogram is also recorded which corresponds to activation of the right ventricular outflow tract

This new approach offers a third alternative to the indirect

cantly ($P < 0.01$) reduced after eight weeks with atenolol therapy compared with placebo

Hansson and colleagues[4] have also evaluated atenolol A multi center trial has been reported which employed a double blind technique without cross over in which patients were randomly allocated to 16 weeks treatment with placebo or atenolol Comparisons of recumbent blood pressure to eval uate the effect of different doses of atenolol showed that a further and significant reduction of diastolic blood pressure occurred when 200 mg was given instead of 100 mg daily ($P < 0.01$) A further increase to 400 mg daily did not produce a further significant reduction in blood pressure The reduc tions of arterial pressure obtained were of the order of 30/15 mm Hg

A further study has been reported recently [5] A double blind cross over trial was undertaken in 24 carefully selected hyper tensive patients After a four week run in period on placebo each patient received atenolol 200 mg /day atenolol 400 mg / day a combination of atenolol 200 mg /day and bendroflua zide 5 mg /day and bendrofluazide alone according to a random sequence At either dose atenolol produced a signifi cantly greater reduction in lying standing and postexercise blood pressure levels except standing systolic pressure than bendrofluazide alone There was no statistically significant difference between the effects of the two atenolol doses on either blood pressure or pulse rate The approximate reduction in blood pressure was 35/22 mm Hg and no further reduction occurred after two weeks on atenolol therapy The addition of bendrofluazide to the lower dose of atenolol resulted in a further significant lowering of the blood pressure As in the two previous studies it is of interest that increasing the dose did not increase the hypotensive effect This has been reported recently with oxprenolol but not with propranolol where the use of higher doses—2 to 5 G per day—has been recommended if an effect is not obtained at low doses say 240 to 360 mg / day

No significant adverse reactions hematological or biochem ical abnormalities were noted in any of the above studies [3-5]

Atenolol has a plasma half life of six to eight hours but demonstrable effects have been shown over longer periods Clinical trials of different doses once daily are in progress These further studies on atenolol alone and on the efficacy of combined treatment with other drugs, and on long term toxicity are awaited with interest as the early work suggests that atenolol is an effective and well tolerated hypotensive agent

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REFERENCES

1 Barrett A M Carter J Fitzgerald J D Hull, L and Lecount D A new type of cardioselective adrenoceptive blocking drug Br J Pharmacol 48 340P 1973
2 Editorial Side effects of practolol, Br Med J 2 57 1975
3 Dollery C T., Lewis G and Myers M G Clinical evaluation of a new beta adrenoceptor antagonist ICI 66082 in essential hypertension Br J Clin Pharmacol 2 185P 1975
4 Hansson L Aberg H Karlberg B E and Westerlund A Controlled study of atenolol in treatment of hyper tension Br Med J 2 367 1975
5 Petrie J C Galloway D B Webster J Simpson W T and Lewis J A Atenolol and bendrofluazide in hypertension Br Med J 4 133 1975
6 Barritt D W Marshall A J and Heaton S Compar ison of oxprenolol and methyl dopa in hypertension Lancet 1 503 1976

A new approach for indirect recording of anterior left atrial activation in man*

Recently considerable progress has been made in the under standing of mechanisms responsible for paroxysmal supraven tricular tachycardia (PSVT) In the majority of cases A V reentrance can be demonstrated The reentrant circuit can be intranodal[1] or involving the normal pathway as the antegrade limb and a manifest or concealed accessory pathway as the retrograde limb of a circus movement One of the techniques used in the catheterization laboratory to localize the site of a retrograde pathway is the mapping of atrial activation sequences during either circus movement PSVT or during right ventricular pacing[3] While the right atrium is easily accessible for catheter mapping the exploration of the left atrium is more difficult since only occasionally can the left atrium be directly entered crossing through a patent foramen ovale Two current indirect methods of left atrial recording include (1) catheterization of the coronary sinus via the right atrium from which a local electrogram can be obtained corresponding to left posterior atrial activation and (2) filtered esophageal electrocardiography a non invasive technique that again permits recording of posterior left atrial activity

Recently we have made the observation that by positioning an electrode catheter in the main pulmonary trunk (Fig 1) a good quality bipolar atrial electrogram can be recorded that is inscribed at the end of the P wave during sinus rhythm This

*Supported in part by USPHS Training Grant No HL-5879 06 and Veterans Administration Grant No 0363 01

Risks of treadmill exercise testing

To the Editor

I read the remarks of G E Burch M D (AM HEART J 91 6 7 19/6) concerning morbidity and mortality on a treadmill annually In the performance of over 550 exercise evaluations on a treadmill we have had no morbidity or mortality The practice of instituting a procedure and policy manual guide lines a to indications of and contraindications to the testing procedure safety regulations certification of those performing and interpreting the test monthly inspection of all equipment used by appropriate electronic specialists the pre exercise interview and physical examination the presence of a physi cian at all times during the test and the post exercise phase should obviate many of these questions

To ensure safety the Connecticut Heart Association has established a Task Force to set such guidelines and attempt to answer the questions

With the predictive data accumulating in the literature in regards to the value of exercise testing and the elimination of false positives and false negatives by careful hi tory physicals and use of ancillary non invasive procedures such as echocardiography multiple leads during exercise testing myocardial perfusion studies i e Thallium ?01 gated blood pool scanning and regional wall motion with radioactive isotopes and systolic time intervals many of the questions are answerable

To ask a question in reverse and one which I feel has more credence How many of the 50 to 60 per cent of sudden deaths that occur annually could be avoided with the proper u e and screening of various subsets of our population presently subject to the epidemic of coronary artery disease?

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REFERENCES

1 Ellestad M H and Wan M K C Predictive implica tions of stress testing Circulation 51 363 1975
2 Ellestad M H Can stress testing predict the severity of coronary disease? Chest 69 ,08 19 6
3 Goldman S Tselos S and Cohn K Marked depth of S T segment depression during treadmill exercise testing Chest 69 ,29 19/6

A spray for pain

To the Editor

I have found a cold spray which is extremely useful to relieve acute and at times even chronic pain It is a mixture of 85 per cent trichloromonofluoromethane (Genetron 11) and 15 per cent dichlorodifluoromethane (Genetron 12) This liquid mixture can be placed in a bottle that sprays a fine stream after being chilled in a household type refrigerator and warmed only slightly by holding the glass bottle in the palm of the hand The best spray bottle for this is the glass bottle used by the Gebauer Company for their ethyl chloride spray The spray is applied as a liquid stream by the physician in a sweeping motion *unidirectionally* in a centrifugal direction along the path of the nerve jud ed to be conducting the pain stimuli The spray should never be applied in a back and forth motion This mixture does not stain or discolor hair and is not toxic (ethyl chloride is) but it should not be allowed to enter the eyes nasal passages or other orifices It can relieve the pain of herpes zo ter sprains acute myositi arthritis cardiac causalgia Tietze syndrome or almost any type of pain The relief can be permanent partial complete or temporary following one application or after several applications Expe rience with its use is most important to establish effectiveness This mixture can be obtained and dispensed by the physician or purchased in spray bottles† from local pharmacies Its use for Tietze syndrome can be rewarding in cardiology but it is advisable to be careful when using it in the patient with ischemic heart disease because of possible reflex coronary vasoconstriction from the associated chill

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All ed Chemical Corporation General Ch m l D vis on
†G bau r s Fluori Meth Sp y

exploration of the left atrium This information should be helpful in those cases in which the coronary sinus cannot be entered In addition it allows mapping of left anterior atrial activation during PSVT Early retrograde activation of this left anterior atrial site would strongly suggest the presence of a left anterior anomalous A V connection

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REFERENCES

1 Wu D and Denes P Mechanisms of paroxysmal supraventricular tachycardia Arch Intern Med **135** 437 1975
2 Wellens H J and Durrer D The role of an accessory pathway in reciprocal tachycardia Observations in patients with and without the Wolff Parkinson White syndrome Circulation **52** 58 1975
3 Svenson R H Miller H D Gallagher J J and Wallace A G Electrophysiological evaluation of the Wolff Parkinson White syndrome Problems in assessing antegrade and retrograde conduction over the accessory pathway Circulation **52** 552 1975
4 Amat y Leon F Dhingra R C Wu D Denes P Wyndham C and Rosen K M Catheter mapping of retrograde atrial activation Observations during ventricular pacing and A V nodal reentrant paroxysmal tachycardia Br Heart J **38** 355 1976
5 Barold S Filtered bipolar esophageal electrocardiography AM HEART J **83** 431 1972
6 Wu D Denes P Amat y Leon F Chablani R C and Rosen K M Limitations of the surface electrocardiogram in diagnosis of atrial arrhythmias Further observations on dissimilar atrial rhythms Am J Cardiol **36** 91 1975

Of rate of pacing old hearts

How rapidly should an old heart be paced with artificial pacemakers? At the same rate as young hearts? The myocardium is muscle just as skeletal muscle is muscle Skeletal muscle of an old man cannot move fast (contract rapidly) Have you ever seen an old man run? Or high jump? Or play basketball? Any farmer knows he would never race an old horse or old mule with its old skeletal muscle Old skeletal muscle should not be raced—even grandmothers know that We know the limits of rapid rates for young hearts But what about old hearts? Should the artificial pacemaker be set at 60 65 70 beats per minute or at what rate for an 80 year old man? I would say Don t drive an old heart too fast The heart usually slows and rests during sleep in young and old people Therefore why drive an old heart at 72 beats per minute or thereabouts all of the time even during sleep?

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REFERENCE

1 Burch G E Relationship of heart rate to cardiac output work power and tension in man JAMA **182** 339 1962

American Heart Journal

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Editorial

Changing concepts in cardiovascular therapy—A quarter century perspective

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There has been considerable increase in cardiovascular research and in clinical cardiology since 1950 More money and more people probably have been directed to the study and management of cardiovascular diseases during the immediate past quarter century than throughout the entire period of the history of medicine and man prior to 1950 But what outstanding advancements have followed this extreme effort in manpower and money? It must be realized at the outset that cardiovascular diseases offer greater and more difficult challenges to medicine than any other disease group More than 50 per cent of the deaths of Americans were due to heart disease prior to 1950 and more than 50 per cent are still due to heart disease today The life expectancy of Americans almost reached a plateau in 1950 and we are still on that plateau if not even a little below it But this does not necessarily mean that changes have not occurred for they have Obviously all of the changes that took place during the past 25 years cannot be included in this presentation so only certain ones have been selected for discussion and critical review

Shortly before 1950 the greatest advancement in cardiovascular therapy occurred That was the introduction of *penicillin* to clinical medicine in adequate amounts and at a price within reach of all Americans This served as a stimulus for the introduction of many new antibiotic agents and methods in antibiotic therapy Since the advent of *penicillin* syphilitic heart disease has been entirely eliminated infections such as bronchopneumonia are no longer the primary cause of death in patients with myocardial infarction and congestive heart failure Prior to 1950 many if not most of these patients died of complicating infections and not of their heart disease Such complications are not the great therapeutic problems today The complex cardiac and cardiopulmonary surgical operations performed today would be impossible to justify were it not for antibiotics to prevent or control operative and postoperative infections Subacute bacterial endocarditis was 100 per cent fatal prior to the advent of penicillin Now it is about 100 per cent curable Of all therapeutic procedures and agents the antibiotics enjoy the greatest therapeutic role in cardiology The extent of the role of antibiotics becomes more evident the more we think about it

Hypertension a disease of millions of Americans is becoming not only readily detected but controlled or even cured since the introduction of many antihypertensive drugs and lay education Much has yet to be done or can be done today in the management of arterial hypertension even though hypertension kills much fewer people than it did prior to 1950 In the field of antihypertensive agents as with antibiotic

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Book reviews

Lethal Diseases of the Ascending Aorta Edited by C F Anagnostopoulos M D Baltimore 1976 University Park Press 150 pages $14 50

This book contains the papers presented at a symposium at the University of Chicago in 1974 Three main subjects were discussed namely (1) coronary artery disease (2) transposition and (3) dissections The material presented is not new to those who follow the medical literature but this 150 page book summarizes in a single volume the opinions of the respective contributors Syphilis of the aorta is not discussed adequately This may be due to its present low incidence in the U S A The panel discussions though brief are good This is a brief but good review of an important subject in medicine

Cardiovascular Problems Perspectives and Progress Edited by Henry I Russek M D Baltimore 1976 University Park Press 478 pages $39 50

This book contains the papers presented at the Seventh Annual Symposium on Heart Disease This annual meeting of Russek is always exciting well done and well attended This book of papers delivered at this meeting in New York City in December of 1974 should interest all physicians who treat patients with heart disease Each year Russek adds another good book to the medical literature May he continue to do this for many more years

Announcements

Changing Seasons of Life

The Continuing Medical Education Institute The Changing Seasons of Life The Physician s Role scheduled for the S S Rotterdam April 23rd through 30th 1977 is sponsored by Sea and Shore Seminars Washington D C The Charles R Drew Postgraduate Medical School The Office of Continuing Education The University of Cincinnati College of Medicine The Office of Continuing Medical Education ,

Medical problems of interest to both specialists and generalists will be presented in a continuum prenatal through geriatric years This course is acceptable for 25 hours in Category I credit for the Physician s Recognition Award AMA Registration $175 00 (after February 23rd 1977 $200 00) Additional professional areas for which accreditation will be available will be sent on request For further information contact Sea and Shore Seminars 2100 19th Street N W No 601 Washington D C 20009 Attn N Chamberlain

Symposium on ancient and modern healing

Health and healing Ancient and modern a weekend symposium cosponsored by the Department of Psychiatry Albert Einstein College of Medicine and The Institute for the Study of Human Knowledge will be held at the Americana Hotel New York City on April 2 and 3 1977 This symposium will attempt to expand the concepts of medicine to include those elements of ancient healing that apply to our culture and current system of health care Topics will include holistic approaches to ancient and contemporary medicine symbolic healing in China Navaho Indian medicine healers of India mind/body relationships in healing biofeedback training and self healing The speakers include René Dubos Ph D Herbert Benson M D Jerome Frank M D Ph D Peter Brent Donald Sandner M D Arthur J Kleinman M D and David S Sobel The symposium is approved for up to 12 hours of Category I credit toward the AMA Physicians Recognition Award Fees are $75 00 regular $85 00 [with credit] and $30.00 for full time students

Further information may be obtained from Dr Mel Roman Department of Psychiatry Albert Einstein College of Medicine 1165 Morris Park Ave Bronx N Y 10461 or by calling (212) 597 1000 ext 201

Teaching seminar on cardiovascular epidemiology and prevention

The Council on Epidemiology and Prevention of the International Society of Cardiology announces its tenth ten day International Teaching Seminar on Cardiovascular Epidemiology and Prevention to be held in Ghana August 21 through September 2 1977 Approximately 30 fellows can be accepted. Final selection will be made by the Council s Seminar Committee Nominees should be at the postdoctoral level, with some residency training or its equivalent and be interested in cardiovascular epidemiology Except in unusual circumstances preference will be given to younger candidates with little or no formal training in epidemiology Limited funds may be available to give partial assistance with travel costs for accepted fellows Room and board are provided without cost to fellows *Fluency in English is an absolute essential*

Three documents are required for application and should be sent at time of application A letter of nomination submitted by chief of department or institution a personal letter of application from the nominee and the applicant s curriculum vitae These should be received prior to the deadline for application May 1 1977 Applications should be sent to Jeremiah Stamler M D Chairman Council on Epidemiology and Prevention ISC Northwestern University Medical School Ward Building—Room 9 105 303 East Chicago Ave Chicago Ill 60611

monitors lines in the patients and drugs Cathode ray oscilloscopes do not make a great CCU but people do

The cardiac pacemaker has been a tremendous therapeutic advancement in clinical cardiology even though the number of patients who benefit from it is relatively small The instrument itself and the methodology are good even though not perfect Again the cardiologist can approach his patient with complete heart block with much to offer He and the cardiac surgeon can assist the patient extremely well when patient selection is clinically logical and not empirical The pacemaker is a real plus in cardiologic therapeutic advancement This is also true for cardiac resuscitation However the latter has produced problems—for example when should resuscitative efforts be discontinued and who should make the decision

The management of cardiogenic shock is still poor It is better by far at present to prevent shock than to try to treat it or cure it Counter pulsations and other therapeutic procedures are still being developed but cardiogenic shock continues to carry a high mortality rate

Coronary angiography and bypass surgery are yet to be fully evaluated There have been enough of both already performed for an unbiased group of statisticians and actuaries to learn what these procedures have to offer patients with ischemic heart disease and which patients are best suited to benefit from them Surely chest pain alone is not an indicator for either or both procedures What are the criteria for either or both? These criteria can be determined from the mass of existing data available for unbiased study There is no need to gather more data for either procedure to evaluate them

One has only to review the program of the 1976 meeting of the American College of Cardiology to appreciate the extent of the activities in cardiology in the immediate past quarter century The impressive exhibit section of the meeting readily revealed what the cardiac patient has confronting him Those doctors who practiced prior to 1950 and who are still in practice could best appreciate the changes and could conclude for themselves what part of that display would be good for his patients and what would not We must be careful that the new complex procedures and fancy displays do not reduce the confidence of the family doctor and the doctor in small towns suburbs and isolated areas of large cities who care for the great masses of people I advise these doctors strongly *not* to lose confidence All of the new gadgets displayed at medical exhibits will never replace sound masterful bedside cardiology and medicine The well trained family doctor who treats the great masses of sick people can walk with pride confidence and satisfaction among all other fellow physicians

In 1948 the great National Heart Institute was born It was about 1950 that the National Institutes of Health began to influence medicine in America and in the World The Heart Institute had a profound influence on changes in cardiology Recently it became the Heart and Lung Institute I should like to indicate strongly and with great satisfaction and pleasure that the Heart Institute and the entire NIH owe their greatness to the mind and vision of Dr C J Van Slyke a career officer of the U S P H S It was he who really developed the double review system of grant evaluation placed and kept NIH in the hands of the scientists who produced the work and generated the ideas Doctor Van planned the organization of NIH and training of successors I pay special tribute to him and also to Dr Franklin Yeager and those who trained under them at the National Heart Institute Dr Van Slyke died too early and of all things of heart disease NIH has been and still is one of the finest branches of our government But NIH is no greater than its people and committees that are responsible for its decisions The people who hold and direct funds in NHLI should realize the seriousness of their responsibility *to people and* science Never must they place themselves above that responsibility Let s keep NIH in the hands of the scientists who depend on it Beware of administrators and politicians (although we need them all especially those like Senator Lister Hill and Congressman John Fogarty) I think the NIH especially the National Heart Institute was given money too fast so that the quality of research in cardiology suffered considerably more than it should have even though the quantity advanced exponentially

The advancements in cardiology during the past quarter century have been great quantitatively Large laboratories and research and clinical service teams can be found all over the USA Almost every small hospital has a CCU monitors defibrillators and other gadgets and special

agents the pharmaceutical industry has blazed the path The pharmaceutical industry has contributed extensively to cardiology during the past quarter century It is this industry to which we owe so much in the treatment of hypertension The physician can now approach his hypertensive patient with confidence and therapeutic logic and plans knowing he can reduce his patient s blood pressure and control it with drugs diet proper living and home recordings of the blood pressure

Cardiac surgery has made tremendous advances Three or four previously incurable cardiac diseases can be cured surgically today and many other patients can be helped considerably What a surgeon can do to the heart today in the operating room would not have been believed possible or even probable prior to 1950 When properly selected, certain patients with cardiac disease now have surgical therapy available for them This was not so prior to 1950 The anesthesiologists and other members of the cardiac surgical teams must be recognized John Gibbon's cardiopulmonary pump made complex heart surgery possible Nevertheless it would be interesting to balance the books in cardiac surgical therapy not for the large centers only but for the entire nation to learn if the net balance is in the black or in the red

Cardiac catheterization has been introduced as a new diagnostic tool in the management of cardiac patients It is my firm opinion that few really new pathophysiologic or hemodynamic advancements were made by cardiac catheterization during the past 25 years yet the procedure does play an exceedingly important role in the management of congenital heart disease, much more so than in acquired heart disease and so called adult heart disease Catheterization procedures and techniques have not been of the highest quality Nevertheless cardiac catheterization remains an advancement in cardiology Its success in clinical medicine for the entire nation also needs detailed critical and unbiased evaluation

Electrocardiography and vectorcardiography have advanced somewhat since 1950 from the theoretic point of view, but these advancements have really influenced cardiac therapy relatively little compared to their great advancements prior to 1950 These diagnostic procedures have been taken for granted for the past 25 years But it was the ECG that made it possible to observe each heart beat in the space program and during man s trek to and from and on the moon

Echocardiography is relatively new in the field of clinical cardiology Its role is yet to be fully developed, evaluated, and exploited It is certain to be employed extensively, but, at present it really has little to offer the master clinical cardiologist who studies his patient well by conventional and less impressive bedside or office practice methods The same may be said of nuclear medicine Both can help with the diagnosis of pericardial effusion and echocardiography can assist with detecting interventricular septal hypertrophy (localized or diffuse) and septal dysfunction Echocardiography is an important addition to cardiology It is safe and the method is sure to be improved This diagnostic method shall develop in a manner similar to electrocardiography

Now we have the treadmill—an expensive diagnostic procedure which is of limited or little assistance to the well trained clinical cardiologist! Patients walk the treadmill by the thousands daily at a great cost to patients insurance companies, and the U S Government But what are the criteria of abnormality? When is the treadmill test indicated? And, why and when should one use a procedure in diagnosis so hazardous that a physician trained in cardiac resuscitation must be in attendance, supported by a monitor defibrillator and potent cardiac drugs and able assistants? The treadmill needs evaluation and this can be done readily with existing data There is no need for any more data Remember it is lucrative financially but is it less hazardous than Red Dye No 2?

The CCU has come into existence since 1950 Is it worth the cost? Can the well trained physician do as well with less costly and more simplified facilities? The convenience of the CCU to the doctor is evident It is comparable in many ways to the ER (emergency room) with the constant availability of physicians nurses aids equipment and supplies But the CCU needs careful and objective evaluation with the idea of effecting a change to reduce cost and increase effectiveness and efficiency in all respects Maybe the present CCU is the best we can do but I doubt it I am impressed more and more with the importance of the qualifications of the personnel—all of the people—and their motivations and less with the

amount of money the institution can provide the scholar to allow him absolute freedom to teach study conduct research and think creatively! The importance and magnitude of this indirect financial support to which administrators devote excessive amounts of time and interest deviate their own attention away from important primary institutional responsibilities of scholarship It is time therefore for all granting agencies to separate the indirect support from the direct grant support and leave the grantee alone and entirely free to think and work The institutions *must* exist and *must* be supported but by a different and less difficult mechanism They should be supported directly in amounts to fulfill their basic needs devoid of frills The frills could be relegated to the resourcefulness energies and motivations of the administrators only of the respective institutions Institutional support and research support should be sharply and clearly separated as one of the efforts to slay the *monster* slowly created in medicine during the past 25 years The sense of values must change if America is to advance scientifically Do we wish to breed grant managers or rather true master scholars and scientists?

The U S Government an institution of people (and people are not infallible) is responsible for a great deal of the financial woes in clinical cardiology and the change in clinical practice Medicare a program of the U S Government allows $20 00 for a history and physical examination which should require at least 1 hour to be obtained properly by a master physician On the other hand Medicare allows $30 00 for a VCG $10 00 to $15 00 for an ECG $175 00 to $450 00 for cardiac catheterization $65 00 for an echocardiogram $42 00 for an apexcardiogram $42 00 for a phonocardiogram $85 00 for a treadmill stress test etc all of which are usually recorded often improperly by technicians (except for cardiac catheterization) without college training and with no imposition on the doctor s time As a result many physicians spend little time with their patients personally and order a number of expensive unnecessary and even hazardous procedures gather large quantities of money and yet render no necessary additional service to the cardiac patients These physicians could have done a great deal more for their patients by talking to them and examining them carefully with the support of selected simple studies such as an ECG and EPA x ray film of the chest CBC urinalysis and a few indicated chemical studies A super cardiologist may receive $20 00 for spending one hour with his patient whereas any surgical procedure of 1 hour duration provides an income of several hundred dollars The cost of renumeration for medical care needs meticulous investigation and redefinition People (all taxpayers included) are being hurt financially by this system of financing the care of heart disease and patients are being hurt both medically and financially The cost of cardiac care needs careful scrutiny The cost certainly can be reduced considerably and primarily through better education of bedside cardiologists and physicians Routine expensive tests result in big money

The U S Government alone now spends over 100 billion dollars in the health field—the life blood of the health monster It is expected therefore that with so much money available many people schemes programs and many other activities will enter into the molding of this tremendous monster which is too big to manage closely and properly

Before new procedures especially costly and hazardous ones are introduced into general use they should be carefully investigated The studies and evaluations for clearance should be as rigid as those for drugs When one or two people or even a rat develops cancer and loses a life the drug that only might have produced the malignancy is immediately removed from the market On the other hand diagnostic and therapeutic procedures with much greater morbidity and mortality are not even seriously questioned Imagine injuring or killing a patient in the process of making a diagnosis! The public depends on all of us both in private and government practice for careful evaluation of all medical procedures and agents During the past 25 years much more expensive hazardous and even fatal or permanently crippling diagnostic and therapeutic procedures have not only entered the practice of cardiology in special centers but are employed extensively throughout the nation even in small rather poorly equipped areas

The excitement concerning anticoagulant therapy was at a peak during the early part of the past quarter century Discussions at medical meetings were primarily concerned with such therapy This excitement has quieted during the last 10 years or so This phenomenon of new ideas and programs

personnel The activities in research and clinical cardiology are considerable and much too numerous to even mention but there are a few problems in cardiology that especially concern me My analysis of these problems may not be correct but I am still concerned about these problems

I ask Have we in the last quarter century created a monster in cardiology? I think we have! Surely not intentionally Beware we have a monster in our environment!

Consider research alone The reviewing and funding system seems to have little confidence or trust in the American scientist himself All investigators regardless of ability are treated alike Too few exceptions are made Venture research receives little if any support Research programs receive support if they conform to existing interests and concern diseases and programs selected by committees and unknown people for emphasis in research Unfortunately the system of grant award requires a detailed outline of the programs in advance including methods and apparatus and anticipated results and importance of their findings—a sort of contract research But this cannot be more than technologic research Little really new knowledge will follow The great advancements in science to date did not occur in this manner How could Roentgen have written his application for funds to discover x rays or Fleming to discover penicillin (in fact Fleming did not realize the importance of his discovery himself others had to show him) or Madame Curie to discover natural radiation or Nicolle to discover polarized light or a 19 year old female graduate student to discover X radiation from outer space or Einstein to create new physical laws by thinking or Gauss to create by thought alone outstanding concepts in mathematics Nicolle did not know the significance of his discovery He surely did not envision the Polaroid Company of America when he discovered polarized light Surely we can afford to support scientists on their own merits alone who can be allowed to think and tinker with ideas free from grant applications reports or lectures We recently supported the Vietnamese refugees a laudable act, but what about the great minds of American scientists? We must have confidence in them One or two may be responsible for a great advancement every quarter century One or two great discoveries and creative thoughts from the minds of American scientists will in turn result in great technologic advancements and [illegible] We must differentiate between technologic research and venture research Grant managers will not make great discoveries They are too busy managing grants For example would 20 scientists free to study think and conduct venture research with $50 000 per year for 25 years each produce more for cardiology than $1 000 000 per year allocated to support a single center grant SCOR grant or MIRU grant for 25 years? The question needs an answer at least an attempt at an answer The data for a critical unbiased analysis are already available Remember the strength and future of America resides in the minds of its people The true scientists should be supported with security to study and think free of pressures imposed by procurement of their own funds annual reports lectures and [illegible] accounting and auditing Americans must have implicit confidence in their few true scientists Let s support people with security and absolute freedom to think

The developments in the last quarter century have produced an unfortunate change Prior to 1950 the universities and research institutions recruited faculty and scientists based on their scientific qualifications and scholarship with full expectations that the administrators would provide their salaries security and financial needs This is now reversed The scientists procure the grants to provide the overhead (indirect costs) to support the administrators who in turn police the budgets of the grant awards The indirect support of these institutions interferes psychologically and administratively with the performance of the grantees This situation has slowly developed during the past 25 years Today another unfortunate factor of extreme importance in recruitment is based upon whether or not the potential appointee can provide his own fund and even his own salary through grant award and the magnitude of overhead he will provide the administrators to meet their needs This 180 degree turn in events is most unfortunate and disarms the true scientist and thinker and his scholarly activities His grant award record is carefully evaluated by the institution s business office whereas his scientific accomplishments are too often ignored or poorly evaluated or not even appreciated Imagine appointing a scholar on the basis of the amount of funds he will provide the institution and administrators instead of the

Coxsackie virus heart disease and cardiomyopathy

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Already in 1964 Burch and DePasquale and Brigden[2] were suggesting that cardiomyopathies might result from old burned out myocarditis This suggestion has been confirmed by many authors [9] One worker suggested that one benefit which could come from an accurate follow up of patients with viral myocarditis is a clue to the riddle of congestive cardiomyopathy The same conclusions were reached by Goodwin [1] who said accurate long term follow up studies of known acute myocarditis to detect chronic cardiac damage are essential

In alcoholic cardiomyopathy the recording of systolic time intervals is a useful method of assessing a preclinical cardiac malfunction In order to determine myocardial performance the patients admitted to our division with Coxsackie virus heart disease 4 and 5 years ago have been re examined by recording the systolic time intervals with a noninvasive standard technique

Methods and results

During the period from November 1969 to December 1971 we identified 22 cases of Coxsackie virus heart disease Viral myocarditis was suspected when clinical and electrocardiographic (ECG) signs of heart disease appeared during an influenza like illness especially when there was pain in the chest aggravated by respiration In these circumstances virus and serum investigations were carried out The virus etiology of the heart disease was proved on the basis of a fourfold or greater rising antibody titre or by the isolation of Coxsackie virus

Eleven subjects with hypertension diabetes chronic alcohol intake or over 35 years of age were eliminated from the trial One patient died immediately after delivery with acute cardiac insufficiency The other 10 patients and 10 normal ambulatory control subjects matched for age and sex were examined 42 to 68 months after the acute illness and polygraphic recordings were made by standard methods of ECG Lead II heart sounds at the cardiac apex and right carotid displacement pulse

The heart sounds were recorded at the cardiac apex after securing the microphone (Battaglia Rangoni TM 1/102) with a rubber belt The carotid pulse was recorded over the maximal external point of pulsation of the right carotid artery (Hellige microphone Mod A Type Bouck Brecht) The ECG phonocardiographic (PCG) and carotid pulse tracings were registered during relaxed mid expiratory apnea on a four channel Battaglia Rangoni oscillograph M 10 at a paper speed of 100 mm per second

The following systolic time intervals were obtained

HR (heart rate in beats per minute)
EMS (electromechanical systole of left ventricle)
LVET (Left ventricular ejection time)
PEP (Pre ejection period)
PEP/LVET

The heart rate (HR) was obtained from the cycle length (R R interval of the ECG) The EMS was measured from the Q wave in Lead II of the FCG to the first high frequency deflection of the aortic component of the second heart sound

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finally reaching a stable mature level is well known to all who have been in the practice of medicine and cardiology since before 1950. This same maturing and stabilizing phenomenon will occur for those exciting popular concepts and programs in cardiology today. The next 25 years will be as interesting and equalizing as the past 25 years, if not more so, since there is more involved at present.

Arteriosclerosis remains the great plague of mankind. Very little if any influence on its incidence has followed the cholesterol investigations and associated therapeutic approaches. Coronary heart disease and arteriosclerotic disease of the brain, kidney, extremities and other structures continue unabated. It is time new ideas and programs be supported with the same vigor and enthusiasm as was the cholesterol concept. Prevention cannot be effectively instituted until the etiology is better known.

There is a need to present medical problems to the lay public through the media in a more direct manner. The extensive presentation of medical information to the public via news media has been one of the important changes in the past 25 years. This change is good. After all, the people are supporting a large portion of the research and development in medicine these days. However, the people's response to the reports through the lay media has been one of disappointment. The public has been made to expect a cure for heart disease, arteriosclerosis or cancer, or an artificial heart at any moment. These cures are yet to come and really none is even on the horizon. An artificial heart was predicted to be available in four years by prominent physicians 10 to 15 years ago. This has not occurred. The people understand the magnitude and difficulties involved but they do not appreciate constant promises with no deliveries to cure their loved ones regardless of the motivations of public proclamations.

We have so much to do as we enter the final quarter of this century. We must exploit the tremendous resources of America and her people to provide great progress and great things to improve the health and happiness of people. We must develop more scientists and let them alone to develop their own programs which are always tailored to their capabilities and their interests and facilities.

People are less happy today in spite of more material wealth. The study of happiness and how to increase it as well as the study of the fundamental biologic process of aging should be included at the top of the list for the final quarter of the 20th century. This twentieth century with its multiple wars and social turmoil and unrest has not been conducive to happiness, at least not during the past 25 years. Let us study happiness and learn to make people happier without requiring that they be materially wealthier.

It has been a great privilege to have lived, seen and participated in the activities of not only the third quarter of the 20th century but of the second quarter as well. It was exciting and interesting even though it was not all good. After all, most of the history of medicine is the history of errors. But advancements are achieved. We must continue to work and try to advance knowledge without ever compromising quality of performance.

December 1971 were re examined after a period of 42 to 68 months from the acute illness The patients with hypertension diabetes chronic alcohol intake or aged over 35 were eliminated from the trial With the purpose of assessing myocardial function the systolic time intervals were recorded by a noninvasive standard technique

The differences in systolic time intervals between the group of patients with previous viral myocarditis and a group of normal control subjects were not statistically significant However the pre ejection period was clearly prolonged in three patients out of 10 a modification consistent with a depressed myocardial function as in patients with cardiomyopathy

Addendum

After submission of this manuscript for publication a left heart catheterization has been carried out in two of three patients with prolonged PEP intervals (the third subject refused the examination) A normal coronarography and a hypertrophy of the left ventricular wall has been demonstrated

The authors are grateful to Dr P Bobba (Istituto di Cardiologia Ospedale S Matteo Pavia Italy) for reporting to them the results of left heart catheterization

REFERENCES

1 Burch G E and De Pasquale N P Cardiomyopathies Viral myocarditis London 1964 J & A Churchill Ltd. pp 3 6-405
2 Bridgen W Cardiomyopathies Other forms of cardiomyopathy London 1964 J & A Churchill Ltd pp 318-321
3 Bengtsson E Myocarditis and cardiomyopathy Clinical aspects Cardiologia 52 108 1968
4 Kawai C Idiopathic cardiomyopathy A study on the infectious immune theory as a cause of the disease Jap Circ J 35 765 1971
5 Sommerville W Postcarditic myocardiopathy Postgrad Med J 48 746 1972
6 Obeyesekere J and Hermon Y Myocarditis after arborvirus infection Dengue and Chikungunya fever Br Heart J 34 821 19 2
7 Gerzèn P Granath A Holmgren B., and Zetterquist S Acute myocarditis A follow up study Br Heart J 34 575 1972
8 Bell E I and Crist N R Enteroviruses and heart disease Cardiol Dig 7 11 1972
9 Whitehead J E M Silent infections and the epidemiology of viral carditis AM HEART J 85 711 1973
10 Editorial Viruses and heart disease Lancet 2 991 1974
11 Goodwin J F Prospects and predictions for the cardiomyopathies Circulation 50 210 1974
12 Spodick D H Pigot D M and Chinfe R Preclinical cardiac malfunction in chronic alcoholism Comparison with matched normal controls and with alcoholic cardiomyopathy N Engl J Med 287 677 19 2
13 Timmis G C Ramos, R G., Gordon S., Pankh, R and Gangadharan V Ethanol induced changes of myocardial performance in healthy adults, Cardiology 59 184 1974
14 Levi, G F and Proto C Coxsackie virus heart disease Lancet 1 598 1971
15 Levi, G F and Proto C Cardiopatia da virus Coxsackie Gior It Cardiol 2 385 1972
16 Weissler A M Harris W S and Schoenfeld C D Systolic time intervals in heart failure in man Circulation 37 149 1968
17 Prapit Sudas Na Ayuthya et al. Coxsackie Group B and primary myocardial disease in infants and children AM HEART J 88 311 19 4
18 Kumar S and Spodik, D H Study of the mechanical events of the left ventricle by atraumatic techniques Comparison of methods of measurement and their significance AM HEART J 80 401 19 0
19 Metzger C C et al True isovolumic contraction time Its correlation with two external indexes of ventricular performance Am J Cardiol 25 434 19 0

Table I Results in normal subjects and in patients with previous Coxsackie virus heart disease*

	HR	EMS	LVET	PEP	PEP/LVET	EMS	LVET
Normal subjects							
Mean	77	379	285	94	0.332	540	414
± S E	4.1	10.9	8.5	7.5	0.031	10.5	11.2
Viral myocarditis							
Mean	76	391	295	101	0.348	548	[illegible]
± S E	4.7	11.5	9.6	8.7	0.034	8.7	[illegible]
Significance (t test)	N S	N S	N S	N S	N S	N S	N S

Units for systolic time intervals are in milliseconds

LVET was taken as the interval from the onset of the rapid upstroke of the carotid pulse to its incisura. PEP was derived as EMS minus LVET. Measurements in five consecutive beats were averaged. The measured values of EMS and LVET were compared with the predicted values for heart rate and sex obtained by Weissler's regression equation (EMS_i and $LVET_i$).[1]

Statistical analysis was carried out with conventional methods for small samples. Differences between the two groups were calculated by the t test. The differences of EMS_i, $LVET_i$, PEP and PEP/LVET in groups of normal subjects and patients with previous Coxsackie virus heart disease were not statistically significant (Table I). However three patients with previous viral myocarditis had clearly abnormal PEP values (118, 125 and 160).

None of the subjects with normal PEP values had cardiorespiratory symptoms or any clinical ECG or x ray evidence of cardiac abnormality. The patients with prolonged PEP values demonstrated an augmented cardiothoracic ratio and minor abnormalities of the ventricular repolarization.

Discussion

Probably there are many causes (alcohol, pregnancy, systemic hypertension, infections) that can produce the clinical and pathological features known as congestive cardiomyopathy.

A systematic demonstration of the connection between infectious myocarditis and congestive cardiomyopathies is lacking. Cardiac abnormalities were reported by Bengtsson[3] in 30 per cent of patients 5 years after suffering from acute myocarditis. Kawai[4] reported statistically significant differences in antibody titres for Coxsackie B and herpes simplex viruses between the patients with idiopathic cardiomyopathy and normal control subjects. The transition from acute illness to a chronic state of congestive cardiomyopathy was described by Sommerville in 10 patients. Obeyesekere and Hermon[8] have shown that patients suffering from dengue and chicungunya fever myocarditis often develop impairment of heart function suggesting the transition to a chronic cardiac disorder. The serologic evidence of a Coxsackie B infection was reported in Thailand by Prapit Sudhas Na Ayuthya and associates[17] in five out of 12 (42 per cent) infants or children with the clinical diagnosis of primary myocardial disease.

In the present series the registration of systolic time intervals demonstrated that 33 per cent of the patients with Coxsackie virus heart disease were examined 4 to 5 years after the acute illness had impaired myocardial function. Three out of 10 patients with previous virus myocarditis had prolonged PEP values. The PEP reflects the isovolumic contraction period; a PEP prolongation, representing a prolonged isovolumic contraction, indicates a decreased rate of contractile element shortening,[1,2] resulting in a decreased contractility or diminished stroke volume. Clearly these abnormalities are entirely consistent with a depressed myocardial function as in patients with cardiomyopathy.

The number of patients is too small to draw any definite conclusions. A second series of patients with Coxsackie virus heart disease (January 1972 to December 1974) will have been reinvestigated by the end of 1976. We think that through long term follow up studies by measuring systolic time intervals in a large number of cases of known Coxsackie virus heart disease, a clue to the riddle of congestive cardiomyopathy may be found.

Summary

Twenty two cases of Coxsackie virus heart disease diagnosed from November 1969 to

ECG recordings were analyzed by a previously described computer system[1] and the total number of premature ventricular contractions (PVC s) the total number of premature atrial contractions (PAC s) the mean number of PVC s per 15 minutes (*mean* PVC s/15) and the mean number of PAC s per 15 minutes (*mean* PAC s/15) during the 24 hour period were determined The accuracy of ectopic counts is verified for each patient by comparing the number counted with the actual number present for randomly selected 1 minute ECG segments during the 24 hours The ambulatory ECG recording was also evaluated for ventricular pairs bigeminy and paroxysmal ventricular and supraventricular tachycardia Maximum heart rate during waking hours was determined and the symptoms recorded in the patient diaries were tabulated Statistical analysis was performed with the two tailed t test for matched pairs to compare the heart rates and number of minutes of treadmill exercise before and during propranolol therapy The per cent change in the number of PVC s and PAC s while the patients were on propranolol therapy was also calculated

Results

Two patients were unable to complete the protocol because of side effects One patient experienced severe dyspnea after 3 days of propranolol 80 mg per day and the other developed severe fatigue after 1 week of propranolol therapy 80 mg per day There was no objective evidence of heart failure in either patient however both patients voluntarily withdrew from the study because of these symptoms The maximum daily dose of propranolol for the remaining 14 patients was 40 mg for one patient 80 mg for two patients 160 mg for seven patients and 320 mg for four patients Propranolol therapy decreased the heart rate on resting ECG from an average of 73 6 ± 10 4 to 59 1 ± 7 4 beats per minute ($p < 0\,001$) and the maximum heart rate on treadmill test from 154 3 ± 17 3 to 120 ± 18 6 beats per minute ($p < 0\,001$) Maximum heart rate on the ambulatory ECG recording decreased from 121 9 ± 14 2 to 97 3 ± 20 2 beats per minute ($p < 0\,005$) These reductions in heart rate suggest that propranolol therapy achieved a significant degree of continuous beta blockade in these patients

Effect of propranolol on symptoms The subjective symptomatic response to propranolol therapy is summarized in Table I Including the two patients who withdrew from the study three patients (19 per cent) considered their over all symptomatic status worse with propranolol therapy The one patient of the three who completed the study noted an increase in chest pain and fatigue each time the dose of propranolol was increased Seven patients (44 per cent) noted no change in over all status with propranolol therapy and six patients (37 per cent) noted improvement with propranolol The major reason for this improvement was a decrease in palpitation in five of the six patients and a decrease in chest pain in the other patient The average duration of propranolol therapy was 13 days in the three patients whose status worsened with propranolol and 4 2 months in the seven patients who showed no change with propranolol therapy This difference primarily reflects the fact that the drug was discontinued promptly in patients who were made worse and discontinued after an adequate trial in those patients who showed no change with propranolol All patients demonstrating initial favorable clinical response remain improved with continuing propranolol therapy with an average follow up of 12 5 months

When propranolol s effect on individual symptom categories is considered (Table I) palpitation present in 12 patients was improved by propranolol in six and unchanged in six Dyspnea present in six patients improved in two was unchanged in four and appeared for the first time in one Fatigue present initially in nine patients

Table I Subjective response to propranolol

	No of patients with symptoms	*Response to propranolol*		
		Worse	*No change*	*Improved*
Over all response	16	3	7	6
Palpitation	12	0	6	6
Dyspnea	6	1	4	2
Fatigue	9	4†	7	1
Light headedness or syncope	7‡	0	3	4
Chest pain	8	1	5	2

*Includes one patient who developed dyspnea for the first time with propranolol

†Includes three patients who developed fatigue for the first time with propranolol

‡Does not include four patients with light headedness or syncope which occurred too infrequently to determine effect of propranolol.

Propranolol for patients with mitral valve prolapse

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Cardiac and noncardiac symptoms including atypical chest pain dyspnea fatigue, palpitation and light headedness or syncope, are frequent among patients with mitral valve prolapse[1-3] These symptoms are usually mild but on occasion may be severe and even disabling Patients with mitral valve prolapse also have a high incidence of atrial and ventricular arrhythmias[4-7] Propranolol has been suggested for relief of symptoms especially chest pain[8,9] and palpitations[10] and for the treatment of arrhythmias[11,12] This study evaluates propranolol s effect on symptoms, arrhythmias and exercise tolerance in patients with mitral valve prolapse

Methods

Sixteen symptomatic patients 14 women and two men, with mitral valve prolapse diagnosed by echocardiogram and/or left ventricular angiogram, were studied after informed consent was obtained The average age was 47 years (range, 30 to 70 years) On the basis of clinical history or coronary arteriography, or both significant coronary artery disease was not evidenced in any of the patients and in all 16 patients mitral valve prolapse was the primary cardiac diagnosis All patients were evaluated for each of the following symptoms palpitation dyspnea, fatigue light headedness or syncope and chest pain Before the administration of propranolol, and at least 5 half lives or a minimum of 72 hours after all cardiac medications had been stopped each patient had a 12 lead electrocardiogram (ECG) a maximal exercise treadmill test with the Bruce protocol[13] and a 24 hour ambulatory ECG recording The results of the control records in many of these patients have been reported previously[4] Patients were included in the present study only if their symptoms were judged severe enough to warrant a trial of therapy During this ambulatory monitoring period the patients recorded all symptoms in a diary Propranolol was then administered daily in four divided doses Initial doses of 40 to 80 mg per day were gradually increased under careful observation until clinical effect, side effect or a dose of 160 mg per day was achieved. Patients with especially severe symptoms or arrhythmias were also evaluated on 320 mg per day The 12 lead ECG, exercise treadmill test and 24 hour ambulatory ECG were all repeated after at least 1 week on the highest dose achieved and in many of the patients at several of the lower doses Each patient was interviewed as to the effect of propranolol on each of the symptoms and the response was scored as "symptom improved" "no change in symptom" or "symptom worse" In addition each patient was asked whether his over all status was improved unimproved or made worse by propranolol therapy

Resting heart rate was determined from the 12 lead ECG s Treadmill tests were evaluated for maximum heart rate achieved flat ST depression of 1 mm or more lasting 0 08 second reason for terminating exercise and total number of minutes of exercise performed Ambulatory 24 hour

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episodes while taking propranolol Thus although propranolol decreased the total number of PAC s it did not appear to decrease the frequency of paroxysmal supraventricular tachycardia

Correlation of symptomatic and antiarrhythmic response to propranolol Five of the six patients reporting a reduction in palpitation had significant antiarrhythmic response to propranolol Four of these had a reduction in PVC s and one had a reduction in PAC s However the relief of palpitation with propranolol was not always related to its antiarrhythmic effect One patient with frequent PVC s and a reduction in palpitation showed no antiarrhythmic effect of propranolol one patient with a 95 per cent reduction in PVC s and elimination of ventricular tachycardia found propranolol ineffective for controlling palpitation

All four of the patients with improvement of light headedness or syncope showed a marked reduction in PVC s with propranolol One of these patients had a clear relationship between light headedness and episodes of ventricular tachycardia one had an episode of light headedness recorded without ECG changes and the mechanism of light headedness was unknown for the other two patients In the three patients in whom light headedness or syncope did not improve with propranolol the symptoms were documented to be functional in two and their etiology was unknown in the third

Effect of propranolol on exercise tolerance Before propranolol therapy these patients exercised for an average of 5 8 ± 2 4 minutes on the treadmill Shortness of breath and/or fatigue were the most frequent reasons for terminating exercise While taking propranolol the patients exercised an average of 5 9 ± 1 8 minutes which was not significantly changed from the prepropranolol values When only the group with overall symptomatic improvement is considered propranolol still did not alter the total number of minutes of treadmill exercise tolerance (6 1 ± 1 4 vs 6 1 ± 2 1 minutes of exercise) The reasons for terminating exercise with propranolol therapy were similar to the reasons for terminating exercise before propranolol therapy Two patients who terminated exercise because of chest pain did so both with and without propranolol Three patients with ischemic ST depression before propranolol therapy demonstrated similar changes with propranolol therapy

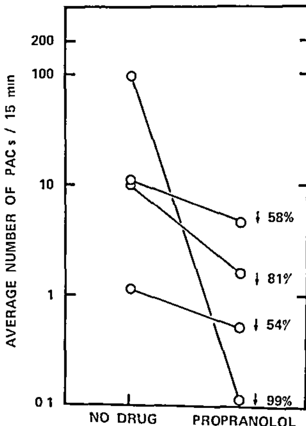


Fig 2 Effect of propranolol on premature atrial contraction (PAC) frequency in the four patients with frequent PAC s The per cent change for each patient during propranolol therapy is given in the right hand column Propranolol reduced PAC s in all four patients Note that the vertical axis showing the *mean* APC s per 15 minutes is a logarithmic scale

Discussion

This study demonstrates a variable response of patients with mitral valve prolapse to propranolol therapy Thirty seven per cent of the patients showed long term symptomatic improvement primarily related to a reduction in the occurrence of palpitation This finding is similar to that of Sloman and associates who found a reduction in palpitation in six of seven patients treated with propranolol In our series six of 12 patients noted a reduction in palpitations and four of seven noted a decrease in light headedness or syncope with propranolol This effect may be related to propranolol s antiarrhythmic action since in five of the six patients with a reduction in palpitation and in all four with a reduction of light headedness it had a marked antiarrhythmic effect However the relief of palpitation was not always related to reduction of arrhythmias Such occa

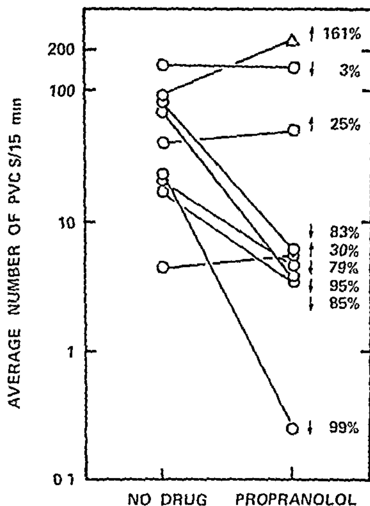


Fig 1 Effect of propranolol on premature ventricular contraction (PVC) frequency in the nine patients with frequent PVC s The per cent change for each patient during propranolol therapy is given in the right hand column Propranolol markedly reduced PVC frequency in five of the nine patients (O) caused no major change in three (O) and increased PVC frequency in one (Δ) The five propranolol responders averaged 90 per cent reduction (range 79 to 99 per cent) in PVC frequency Note that the vertical axis showing the *mean* PVC s per 15 minutes is a logarithmic scale

was improved in one unchanged in seven and worse in one Three additional patients developed fatigue for the first time with propranolol therapy Light headedness or syncope occurred frequently enough to evaluate its response to propranolol in seven patients Propranolol decreased or eliminated these episodes in four patients and did not alter their frequency in three patients Chest pain present in eight patients before propranolol therapy was improved in two unchanged in five and worse in one

Symptoms recorded in patients diaries during ambulatory ECG recordings are summarized in Table II Propranolol reduced the total number of symptomatic episodes recorded by 42 per cent, with 19 episodes recorded before propranolol

Table II Symptoms recorded in ambulatory ECG diary

	No of episodes recorded during ambulatory ECG	
	Pre propranolol	*Propranolol*
Palpitation	7	3
Dyspnea	2	0
Fatigue	2	2
Dizziness	2	1
Chest pain	6	5
Total number of symptomatic episodes	19	11

therapy and 11 while taking propranolol. The number of episodes in each symptom category was too small to indicate meaningful conclusions

Effect of propranolol on ventricular arrhythmias Nine patients had frequent PVC s on the ambulatory ECG recording before propranolol therapy Propranolol produced a 75 per cent or more reduction in the *mean* PVC s/15 in five of the nine patients (Fig 1) The average reduction in the total number of PVC s in 24 hours in these five patients was 90 ± 8 per cent (range, 78 to 99) Three patients showed no major change in PVC frequency with propranolol therapy and one patient had a striking increase in PVC frequency Three of the five propranolol responders had PVC s which were more frequent at higher rate Interestingly the patient showing the marked increase in PVC frequency with propranolol therapy was the single patient completing the study who noted an over all worsening of symptoms Propranolol abolished paroxysmal ventricular tachycardia in three of four patients and eliminated ventricular pairs in four of nine patients However propranolol eliminated bigeminy in only one of six patients The decrease in complex arrhythmias occurred in the five patients who had a reduction in PVC frequency

Effect of propranolol on atrial arrhythmias The response to propranolol in the four patients with frequent PAC s on ambulatory ECG is shown in Fig 2 All four patients demonstrated a reduction in *mean* PAC s/15′ with a 73 ± 21 per cent (range 54 to 99) average reduction in total number of PAC s in 24 hours There were eight episodes of paroxysmal supraventricular tachycardia in these patients before propranolol and 10

improve and in three patients appeared for the first time during propranolol therapy. Premature ventricular contractions were reduced by at least 75 per cent in five of nine patients (56 per cent) and paroxysmal ventricular tachycardia was eliminated in three of four patients. We conclude that propranolol is not uniformly effective in patients with mitral valve prolapse. A trial of propranolol may be instituted for patients with mitral valve prolapse who have severe symptoms and/or arrhythmias but the drug should only be continued in those who demonstrate clinical and/or antiarrhythmic response.

REFERENCES

1. Hancock E W and Cohn K The syndrome associated with midsystolic click and late systolic murmur Am J Med 41 183 1966
2. Barlow J B Bosman C K Pocock W A et al Late systolic murmurs and non-ejection (mid late) systolic clicks. An analysis of 90 patients Br Heart J 30 203 1968
3. Fontana M E Pence H L Leighton R F et al The varying clinical spectrum of the systolic click late systolic murmur syndrome Circulation 40 807 1970
4. Winkle R A Lopes, M G Fitzgerald J W et al Arrhythmias in patients with mitral valve prolapse Circulation 52 73 1975
5. Kreisman K Kleiger R Schad N et al Arrhythmia in prolapse of the mitral valve Circulation 43 44 (Suppl II) II 44 1971 (abst)
6. Gooch A S, Vicencio F, Maranhao V, et al Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome Am J Cardiol 29 611 1972
7. DeMaria A N, Amsterdam E Vismara L A et al The variable spectrum of rhythm disturbances in the mitral valve prolapse syndrome Circulation 49 50 (Suppl. III) III 272 1974 (abst)
8. Jeresaty R M Mitral valve prolapse-click syndrome Progr Cardiovasc Dis 15 623 1973
9. Leatherman L L Armbrust C A Hall, R J et al Chest pain and abnormal postexercise ECG s with normal coronary arteriograms in patients with click-late systolic murmur syndrome Texas Med 69 44 1973
10. Sloman G Stannard M Hare W S C et al Prolapse of the posterior leaflet of the mitral valve Israel J Med Sci 5 727 1969
11. Sloman G Wong M and Walker J Arrhythmias on exercise in patients with abnormalities of the posterior leaflet of the mitral valve Am Heart J 83 312 1972
12. Zeilenga D W, and Criley J M Mitral valve dysfunction—a possible cause of arrhythmias in the prolapsed posterior leaflet syndrome Clin Res 21 243 1973 (abst)
13. Doan A E Peterson D R Blackmon J R et al. Myocardial ischemia after maximal exercise in healthy men Am Heart J 69 11 1965
14. Fitzgerald J Clappier R R and Harrison D C Small computer processing of ambulatory arrhythmias in Computers in Cardiology IEEE meeting Bethesda 1974 pp 31 36
15. Khullar S C and Leighton R F Myocardial lactate production in mitral valve prolapse syndrome Circulation 49 50 (Suppl III) III 237 1974 (abst)
16. Gianelly R E Goldman R H Treister B et al Propranolol in patients with angina pectoris Ann Intern Med 67 1216 1967

sional discrepancies between propranolol's antiarrhythmic action and its effect on symptoms are probably due to the fact that patients with mitral prolapse may have palpitation and light headedness which are not caused by arrhythmias.[4]

Propranolol improved chest pain in only two of eight patients (25 per cent). This low incidence of chest pain relief is similar to the experience of Sloman and associates,[10] who found chest pain to be well controlled by propranolol in only three of eight patients. It differs, however, from the observation of Jeresaty,[8] who found propranolol beneficial in eight of 10 mitral prolapse patients with chest pain. Despite reports which suggest that the pain in patients with mitral prolapse may be ischemic in origin,[15] in our experience the relief of chest pain by propranolol in these patients is less frequent than that seen in patients with chest pain caused by coronary artery disease.[16]

Using our computer system which detects and quantitates PVC's, we were able to demonstrate that propranolol reduced PVC frequency in five of nine (56 per cent) and eliminated ventricular tachycardia in three of four patients. The fact that PVC's were heart rate related in three of these five patients suggests that negative chronotropism may be a major antiarrhythmic action of propranolol. Propranolol reduced PAC's in four of five patients, however, it did not appear to suppress episodes of paroxysmal supraventricular tachycardia. This disparity may be due to the fact that the occurrence of paroxysmal supraventricular tachycardia is not related to the frequency of PAC's', thus decreasing the total number of PAC's would not necessarily be expected to decrease the likelihood of paroxysmal supraventricular tachycardia.

This study did not utilize a placebo control and the subjective response of the patients may have been influenced to some extent by this fact. However, since most over-all symptomatic improvement occurred because of a reduction in palpitation which was associated with an objectively measured decrease in arrhythmias, it seems reasonable to conclude that this improvement was related to the effect of propranolol.

Rarely, sudden death occurs in patients with mitral valve prolapse[1, 8] and occasionally patients present with life threatening arrhythmias. Based on the antiarrhythmic activity of propranolol demonstrated in this study, these patients have a reasonable chance of responding to propranolol therapy. Ambulatory monitoring should be used to characterize the arrhythmias before treatment and then repeated to determine propranolol's effect on them. If propranolol is ineffective in controlling symptoms or life threatening arrhythmias, the drug should be discontinued and alternative therapy evaluated. Whether or not one should treat asymptomatic arrhythmias in these patients is unknown at the present time. If propranolol therapy is considered for asymptomatic patients with ventricular arrhythmias, one should carefully document that the drug is not causing adverse side effects and that it is indeed suppressing the arrhythmia.

Propranolol does not improve, and may in fact cause, symptoms of fatigue. In our study, propranolol did not alter the ability to perform on the treadmill, even among patients who noted symptomatic improvement with propranolol therapy. Thus, propranolol is not a 'tonic' that improves the general well being of patients with mitral valve prolapse.

The variable response of patients with mitral valve prolapse to propranolol requires that therapy be individualized. Symptoms and/or arrhythmias should be characterized before administering propranolol, the effect of therapy carefully determined, and propranolol continued only if it is effective in their treatment. Based on currently available data, indiscriminate use of propranolol in patients with mitral valve prolapse is clearly not justified. An individualized approach will allow propranolol's use in patients who benefit from this therapy and avoid its use in patients for whom it is ineffective.

Summary

This study evaluates propranolol's effect on symptoms, arrhythmias, and exercise tolerance in 16 patients with mitral valve prolapse. Three patients (19 per cent) experienced symptomatic deterioration with propranolol therapy, seven (44 per cent) were unchanged, and six (37 per cent) noted an over-all symptomatic improvement primarily due to a reduction in palpitation. Symptomatic improvement continues in these six patients an average of 12.5 months after beginning propranolol therapy. Treatment with propranolol alleviated chest pain in only two of eight patients and it did not improve the ability to perform treadmill exercise. Fatigue did not

improve and in three patients appeared for the first time during propranolol therapy Premature ventricular contractions were reduced by at least 75 per cent in five of nine patients (56 per cent) and paroxysmal ventricular tachycardia was eliminated in three of four patients We conclude that propranolol is not uniformly effective in patients with mitral valve prolapse A trial of propranolol may be instituted for patients with mitral valve prolapse who have severe symptoms and/or arrhythmias but the drug should only be continued in those who demonstrate clinical and/or antiarrhythmic response

REFERENCES

1 Hancock E W and Cohn K The syndrome associated with midsystolic click and late systolic murmur Am J Med 41 183 1966
2 Barlow J B Bosman C K Pocock W A et al Late systolic murmurs and non-ejection (mid late) systolic clicks An analysis of 90 patients Br Heart J 30 203 1968
3 Fontana M E Pence H L Leighton R F et al The varying clinical spectrum of the systolic click late systolic murmur syndrome Circulation 40 807 1970
4 Winkle R A Lopes M G Fitzgerald J W et al Arrhythmias in patients with mitral valve prolapse Circulation 52 73 1975
5 Kreiman K Kleiger R Schad N et al Arrhythmia in prolapse of the mitral valve Circulation 43 44 (Suppl II) II-44 1971 (abst)
6 Gooch A S Vicencio F., Maranhao V., et al Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome Am J Cardiol. 29 611 1972
7 DeMaria A N Amsterdam E Vismara L A et al The variable spectrum of rhythm disturbances in the mitral valve prolapse syndrome Circulation 49 50 (Suppl III) III 232 1974 (abst)
8 Jeresaty R M Mitral valve prolapse click syndrome Progr Cardiovasc Dis 15 623 1973
9 Leatherman L L Armbrust C A Hall R J et al Chest pain and abnormal postexercise ECG's with normal coronary arteriograms in patients with click-late systolic murmur syndrome Texas Med 69 44 1973
10 Sloman G Stannard M Hare W S C et al. Prolapse of the posterior leaflet of the mitral valve Israel J Med Sci 5 727 1969
11 Sloman G Wong M and Walker J Arrhythmias on exercise in patients with abnormalities of the posterior leaflet of the mitral valve Am Heart J 83 312 1972
12 Zeilenga D W and Criley J M Mitral valve dysfunction—a possible cause of arrhythmias in the prolapsed posterior leaflet syndrome Clin Res 21 243 1973 (abst)
13 Doan A E Peterson D R Blackmon J R et al Myocardial ischemia after maximal exercise in healthy men Am Heart J 69 11 1965
14 Fitzgerald J Clappier R R and Harrison D C Small computer processing of ambulatory arrhythmias in Computers in Cardiology IEEE meeting Bethesda 1974 pp 31 36
15 Khullar S C and Leighton R F Myocardial lactate production in mitral valve prolapse syndrome Circulation 49 50 (Suppl III) III 232 1974 (abst)
16 Gianelly R E Goldman R H., Treister B et al Propranolol in patients with angina pectoris Ann Intern Med 67 1216 1967

Echocardiographic manifestations of annulo-aortic ectasia Its "paradoxical" motion of the aorta and premature systolic closure of the aortic valve

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Annulo aortic ectasia is a morphological term which designates a lesion with a dilatation of the annulus of the aortic valve and fusiform aneurysm of the ascending aorta terminating proximal to the origin of the innominate artery [1] The basic histological lesion is cystic medial necrosis as previously described by Erdheim and is accompanied by other somatic stigmas of Marfan s syndrome in most cases

There are only a few echocardiographic reports on annulo aortic ectasia and they merely describe dilatation of the aortic root as a manifestation [1] We performed echocardiographic studies on patients with annulo aortic ectasia and found not only dilatation of the aortic root but also unusual motion of the aortic wall and aortic valve

Subjects and methods

There were 12 subjects Eleven of them exhibited skeletal and/or ophthalmic findings of Marfan s syndrome One lacked both and was thought to have *forme fruste* [1] Ten were male and two were female Their ages ranged from 10 to 55 years the mean age being 33 years The existence of annulo aortic ectasia in all cases was proved by angiocardiography and/or surgery (Fig 1) As control groups 20 normal subjects (22 to 36 years mean age 31) and 16 patients with rheumatic aortic regurgitation (18 to 44 years mean age 30) were selected

Echocardiographic equipment was a commercially available Ultrasonic Cardiograph Model WM 09 made by Sanei Sokki and a 2 25 MHz transducer 12 mm in diameter The technique of recording the echocardiogram of the aortic and mitral valve and the method of M mode scan have been described previously [8] The aortic root diameter was measured from the anterior edge of the anterior aortic wall echo to the anterior edge of the posterior aortic wall echo at the end of ventricular diastole when the aortic valve first appeared in the aortic root while scanning between the mitral and aortic root This method was adopted because of variable measurement values of the aortic root diameter especially in annulo aortic ectasia, when the transducer is tilted in a cephalad direction

Results

Aortic root diameter The aortic root diameter at the end of diastole was 2 9 ± 0 35 cm (range 2 5 to 3 5 cm) in the normal subjects 3 6 ± 0 37 cm (range 3 0 to 4 3 cm) in aortic regurgitation and 4 2 ± 0 52 cm (range 3 2 to 5 0 cm) in annulo aortic ectasia The values were statistically significant for each group ($p < 0\ 005$)

Motion of aortic root In the control groups both the anterior and posterior walls showed almost parallel forward motion after the maximum opening of the aortic valve and continued to

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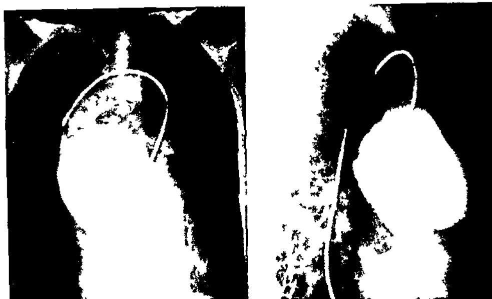


Fig 1 Angiocardiograms show pear shaped dilatation of the ascending aorta and aortic regurgitation jet Left anteroposterior view right lateral view

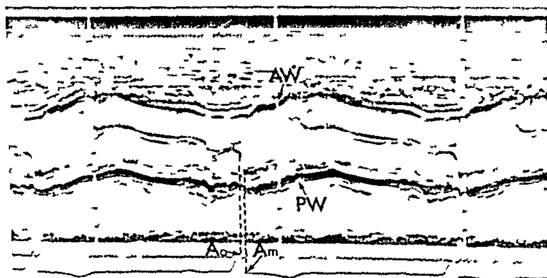


Fig 2 Rheumatic aortic regurgitation Both anterior (*AW*) and posterior (*PW*) walls show a parallel forward motion after the maximum opening of the aortic valve leaflets (*Am*) The onset of the opening (*Ao*) is coincident on the R wave of the ECG (early opening) Diastolic cusp separation (*S*) is observed The distance between two consecutive vertical and horizontal dots equals 1 cm and 1 second respectively

do so for a while after the aortic valve closed (Fig 2) However in annulo aortic ectasia very unusual motion of the wall was observed (Fig 3) The posterior wall exhibited backward motion even after the maximum opening of the aortic valve and this continued until middle ejection This motion is apparently opposite to that of the control groups and appears paradoxical This type of paradoxical motion was observed in eight cases The remaining cases showed almost parallel motion although in three of four cases the posterior wall appeared somewhat flat when compared with the anterior wall Fig 4 is an echocardiogram of this same patient after sur

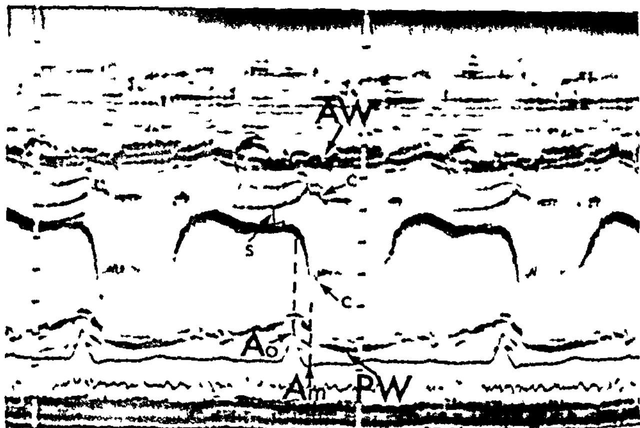


Fig 3 Annulo aortic ectasia The posterior wall of the aortic root shows backward ("paradoxical") motion during early to middle ejection period The *aortic valve leaflets show premature systolic closure (C)* early opening and diastolic cusp separation See Fig 2 for abbreviations

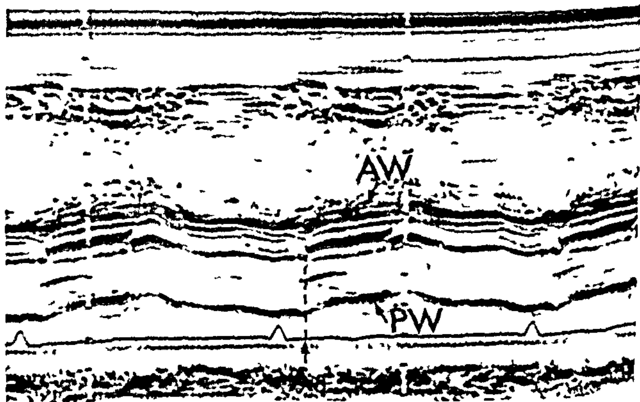


Fig 4 Postoperative echogram Abnormal motion is no longer present Both anterior and posterior walls show a parallel *forward* motion Prosthetic valve opens appreciably after the QRS of the ECG See Fig 2 for abbreviations

gical correction by the method of Singh and Bentall[10] The abnormal systolic motion is no longer present and both anterior and posterior walls show parallel forward motion The aortic root diameter revealed more dilatation in the cases of paradoxical types than parallel types and values were statistically significant ($p < 0.005$) (Fig 5)

Aortic valve The aortic valve leaflets opened rapidly with the onset of systole and then exhib ited abrupt premature partial closure immedi ately after ventricular ejection (Fig 3) The closure occurred consistently right after the cusps opening in all cases and was never seen during middle or late systole The onset of the opening of the abnormal valve is almost coincident on the R waves of the electrocardiogram and reached a fully open position at the J point of the QRS A similar opening was also observed in rheumatic aortic regurgitation (Fig 2) Usually the aortic valve opens at an average of 112 msec after the Q wave this is apparently early opening The postoperative echocardiogram (Fig 4) shows that the Bjork Shiley prosthetic valves reached a fully open position appreciably after the QRS The early opening was in all but one instance with a comparatively small aortic valve annulus diam eter and where aortic regurgitation and diastolic cusp separation have not been recognized yet

Atrioventricular valves There were no specific findings for annulo aortic ectasia Diastolic flut tering of the mitral valve was observed in four cases and systolic prolapse of the mitral valve in one case There was no abnormal motion in the tricuspid valve

Discussion

In annulo aortic ectasia the aortic root diam eters showed a remarkable dilatation and they exceeded that of the rheumatic regurgitation group When the aortic root diameter measures more than 4 0 cm it is necessary to pay attention to the motion of the aortic wall and aortic valve leaflets and to suspect annulo aortic ectasia

We assume that histological changes of the aortic wall greatly contribute to the cause of abnormal motion of the aortic wall It is a well known fact that cystic medial necrosis of the aortic wall is frequently associated with Marfan s syndrome resulting in a decreasing of the elas ticity of the wall Consequently the aortic wall expansion in annulo aortic ectasia appears to be

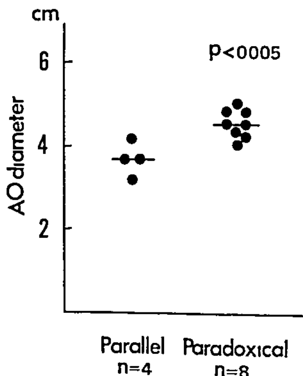


Fig 5 Aortic root diameter vs aortic wall motion "Paradox ical" type shows a more dilated diameter than parallel type *AO* = aortic root

more influenced by the blood flow and/or turbu lence around the markedly dilated sinus of Valsalva than a normal aortic wall Yuste and associates[2] reported an echocardiogram with dissecting aneurysm of the ascending aorta in which the posterior wall exhibited posterior motion during early to middle systole Even though the etiology is different this phenomenon is similar to that of annulo aortic ectasia from the viewpoint of a decreasing of elasticity of the aortic wall Assuming that the abnormal motion of aortic wall is caused by the above mentioned factor the cases that now present parallel type have the possibility of showing paradoxical type with the progression of the histological changes and a decreasing of elasticity of the aortic wall

The premature systolic partial closure of the aortic valve is thought to be caused by a completely different hemodynamic change as seen in idiopathic hypertrophic subaortic steno sis or discrete subaortic stenosis[4] which has a dynamic obstruction in the left ventricular outflow tract Recently Chandraratna and asso ciates[3] reported a similar closing motion in a

patient with a floppy' aortic valve This fact may suggest that the closure is due to the redundant aortic valve leaflets frequently associated with Marfan's syndrome However we and other authors observed such a closure in the patients with ruptured[16] and even unruptured sinus of Valsalva aneurysm, a deformity of aneurysmal dilatation of the sinus of Valsalva also seems to be compounded by either the lower pressure system or a more augmented pull back mechanism

The mechanism of early opening of the aortic valve is far conclusive Since the electrical systolic events precede the mechanical systolic events the aortic valve normally opens after the QRS However, in the patients with annulo aortic ectasia and in some cases of rheumatic aortic regurgitation this unusual motion was observed Very similar motion is also observed in the echocardiogram reported by DeMaria and associates[5] and Feigenbaum[9] The common echocardiographic findings in all cases is the presence of the diastolic cusp separation which has been described as one of the findings of aortic regurgitation[17], an incomplete coaptation of the aortic valve leaflets during diastole may be one of the contributing factors This is only speculation that awaits definitive explanation

We could not obtain findings specific to annulo aortic ectasia from the motion of the atrioventricular valves An interesting point is the incidence of systolic prolapse of the mitral valve Brown and associates[18] reported that among 35 cases with Marfan s syndrome, they found a leaflet prolapse in 32 cases On the contrary we recorded only one case among 12 This discrepancy is probably due to a different left ventricular volume Fontana and associates[11] speculated that the degree of mitral valve prolapse is closely related to the left ventricular end diastolic volume and an increase of ventricular volume would produce more tension on the mitral valve leaflets and chordae by increasing the distance between the ventricular wall and papillary muscles and the valve ring and later and less leaflet prolapse would then result during systole When this hemodynamic mechanism is applied to annulo aortic ectasia with a markedly dilated left ventricle due to severe aortic regurgitation the end diastolic volume is increased and therefore the degree of mitral valve prolapse decreases and possibly disappears as annulo aortic ectasia progresses The only case with a prolapsing mitral valve is the one with a comparatively small aortic valve annulus where aortic regurgitation has not been recognized yet and in addition we have found a mitral valve prolapse in four out of five other cases of Marfan s syndrome which were not included in this study because of the absence of annulo aortic ectasia

In conclusion, our data indicate that echocardiography provides a reliable, sensitive and practical noninvasive means of accurately diagnosing annulo aortic ectasia with abnormal motion of the aortic wall and aortic valve

Summary

The echocardiographic features of annulo aortic ectasia were studied in 12 patients Eleven of them exhibited skeletal and/or ophthalmic findings of Marfan s syndrome and one was considered as having *forme fruste* Echocardiograms revealed not only marked dilatation of the aortic root but also unique motion of the aortic wall and aortic valve Posterior motion of the posterior aortic wall during early to middle ejection period i e, paradoxical motion was noted in eight cases, and premature systolic partial closure of the aortic valve was seen in all case

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REFERENCES

1 Ellis P R Cooley D A and De Bakey M E Clinical considerations and surgical treatment of annulo aortic ectasia Report of succe ful operation J Thorac Cardiovasc Surg **42** 363 1961
2 Erdheim J Medionecrosis aortae idiopathica cystica Virchows Arch Pathol Anat **276** 187 1930
3 Chapman D W Beazley H L Peterson P K Webb J A and Colley D A Annulo aortic ectasia with cysti medial necrosis Diagnosis and surgical treatment, Am J Cardiol **16** 679 1965
4 Kronzon I Weisinger B and Glassman F Cystic medial necrosis with severe aortic root dilatation Che t **66** 79 1974
5 DeMaria A N King J F Salel A F Caudill C C Miller R R and Mason D T Echo raphy and phonography of acute aortic regurgitation in bacterial endocarditis Ann Intern Med **82** 329 1975
6 Winsberg F Aortic valve *in* Gramiak R and Wasg R C Editors Cardiac ultrasound St Louis 1975 The C V Mosby Company p 84
7 Golden R L and Lochin H The forme fru te in Marfan s syndrome N Engl J Med **260** 797 1959
8 Gramick R and Shah P M Echocard ography of the normal and diseased aortic valve Radiology **96** 1 1970
9 Feigenbaum H Echocardiography Philadelphia 19 Lea & Febiger Publishers pp 25 86
10 Singh M P and Bentall H H Complete replacement of the ascending aorta and the aortic valve for the

treatment of aortic aneurysm J Thorac Cardiovasc Surg 63 918 9 2
11 Sakamoto T, Matsuhisa M and Havashi T Fchocardiographic and phonocardiographic measurement of systolic time intervals Cardiovasc Sound Bull 5 63 19 5
12 Yuste P Aza V Minguez I Cerezo L and Martinez Bordiu C Dissecting aortic aneurysm diagnosed by echocardiography A pre and postoperative study Br Heart J 36 111 1974
13 Tajik A J and Giuliani E R Echocardiographic observations in idiopathic hypertrophic subaortic stenosis Mayo Clin Proc 49 89 1974
14 Davis R H Feigenbaum H Chang S Konecke L L and Dillon J C Echocardiographic manifestations of discrete subaortic stenosis Am J Cardiol 33 2 7 1974
15 Chandraratna P A N Samet P Robinson M J and Byrd C Echocardiography of the "floppy" aortic valve Report of a case Circulation 52 9 9 1975
16 Johnson M L Warren S G Waugh R A Kisslo J A Sabiston D C, and Lester R G Echocardiography of the aortic valve in non rheumatic left ventricular outflow tract lesions Radiology 112 677 1974
17 Feizi O Symons, C and Yacoub M Fchocardiography of the aortic valve Studies of normal aortic valve aortic stenosis aortic regurgitation and mixed aortic valve disease Br Heart J 36 341 1974
18 Brown O R DeMots H Kloster F E Roberts A Menashe V D and Beals R K Aortic root dilatation and mitral valve prolapse in Marfan s syndrome An echocardiographic study Circulation 52 651 1975
19 Fontana M E Wooley C F Leighton R F and Lewis R. P Postural changes in left ventricular and mitral valvular dynamics in the systolic click late murmur syndrome Circulation 51 165 19 5

Studies on digitalis

XIII A PROSPECTIVE STUDY OF 649 PATIENTS ON MAINTENANCE TREATMENT WITH DIGITOXIN

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Digitalis intoxication has for many years been known to be very common and serious Many retrospective studies have been carried out to show an incidence of digitalis intoxication ranging from 8 to 20 per cent in hospitalized patients with a mortality rate ranging from 7 to 50 per cent The mortality rate attributed to cardiac toxicity from digitalis ranged from 3 to 21 per cent[1]

Only five prospective studies on the prevalence of digitalis intoxication have been carried out previously Shapiro and associates found an incidence of digitalis toxicity of 18 4 per cent among 441 patients treated with digoxin Hurwitz and Wade[3] found signs of toxicity in 19 8 per cent of 192 patients treated with digoxin Beller and associates[4] observed digitalis toxicity in 23 per cent of 134 hospitalized patients The mortality rate was twice as high in the toxic group as in patients not intoxicated Evered and Chapman[5] found evidence of digitalis toxicity in 22 of 108 patients on digoxin maintenance therapy (21 6 per cent) Howard and associates[6] found an incidence of 13 toxic among 86 patients using digoxin (15 per cent)

Digitoxin has been the cardiac glycoside most commonly used in Norway for many years Our clinical impression has been that digitalis toxicity is not so commonly seen as previously reported

We therefore wanted to study the prevalence of digitalis toxicity in patients on maintenance therapy with digitoxin as only nine patients using this glycoside are included in the prospective studies mentioned above[1]

We further wanted to investigate the specificity of commonly accepted signs and symptoms of digitalis toxicity the influence of sex age, weight accompanying diseases and biochemical disturbances on the appearance of digitalis toxicity Finally we wanted to study the value of determination of serum concentration of digitoxin as an index of digitalis toxicity

Material and methods

During the period from March 1972 to June 1973 all patients on maintenance therapy with digitoxin for more than 3 weeks were evaluated on hospital admission They were classified according to etiology of cardiac disease simultaneously recording diseases of other organ systems especially pulmonary, kidney liver, intestinal and thyroid diseases Patients with suspected or proved acute myocardial infarction were excluded from the study They were placed in functional classes according to the classificaton of the New York Heart Association Their daily dose of digitoxin was recorded and it was noted if they were taking other drugs especially diuretics antihypertensives antiepileptics β blockers quinidine procainamide or sympatheticomimetic drugs

On admission extracardiac symptoms indicating digitalis toxicity were recorded Nausea vomiting diarrhea, anorexia muscular weakness

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neuralgia psychosis delirium color vision blurred vision

Electrocardiographic (ECG) signs of digitalis toxicity were sought for extrasystoles especially ventricular premature beats and it was noted if they were multifocal or unifocal more than 5 per minute ventricular tachycardia or fibrillation atrial tachycardia with block junctional tachycardia with a ventricular rate above 80 atrial flutter or fibrillation with a ventricular rate below 50 A V block S A block with junctional rhythm below 50 sinus bradycardia below 50

According to the presentation of symptoms and signs indicating digitalis toxicity on admission the patients were diagnosed as toxic suspected toxic or nontoxic

On admission a battery of laboratory tests were taken (Table VI) and serum concentration of digitoxin was determined by the Rb method as modified by Gjerdrum

In patients initially diagnosed as toxic or possibly intoxicated digitoxin was withheld for 6 days In a few patients symptoms/signs of toxicity were reduced in severity but still persisted after 6 days Digitoxin was then withheld for 4 more days A final diagnosis was made according to the following criteria

1 *Digitalis intoxicaton* Disappearance of extracardiac and/or cardiac signs of toxicity within 6(10) days after discontinuance of digitoxin

2 *Suspected intoxication* Persistence of extracardiac and/or cardiac signs of toxicity after 6(10) days in spite of discontinuance of digitoxin

3 *Nontoxic* Absence of extracardiac or cardiac signs of toxicity

After 6(10) days a definite diagnosis of toxicity or nontoxicity was made and digitalis medication was resumed A repeat serum digitoxin determination was made after 6(10) days The serum concentration of digitoxin on admission was not known until the final diagnosis of toxicity was made

Statistics Paired observations were analyzed statistically by Student s t test

Results

Presentation of the whole patient material and subdivision into toxic suspected toxic and nontoxic patients are found in Tables I to VIII

Table I Prevalence of digitalis intoxication at hospital admission in 649 patients on maintenance treatment with digitoxin

Digitalis toxicity	*No of patients*	*Percentage*
Definite	39	5 8
Suspected	74	13 1
None	536	81 1
Total	649	100 0

Complete data were available in the charts from 658 patients Nine patients who had symptoms indicating digitalis toxicity were lost to follow up after 6 days in most cases because they had left the hospital They had a mean digitoxin serum concentration of 20 ng per milliliter compared to 16 7 ng per milliliter for the whole patient material In the following presentation these nine patients will be left out The patient material under discussion thus consists of 649 patients 39 of these were toxic (5 8 per cent) 74 were suspected toxic on admission (13 1 per cent) and 536 were nontoxic when first admitted to the hospital Thus 610 patients were finally evaluated as nontoxic (94 2 per cent) (Table I)

Clinical data We see (Table II) that toxic patients are somewhat older than the suspected toxic and nontoxic patients but the difference is statistically not significant There are comparatively more women than men in the toxic group whereas there are more men than women in the suspected toxic and nontoxic groups but the differences are statistically not significant The nontoxic patients are somewhat taller than the toxic and the suspected toxic but the difference is significant only between suspected and nontoxic patients ($p < 0.04$) On the other hand there is a significantly lower weight in the toxic than in the nontoxic patients ($p < 0.05$)

Table II shows that valvular heart disease is the dominant etiologic group in this patient material (56 1 per cent) This is due partly to the fact that the medical department with the larger part of patients in this study is a referral hospital for hemodynamic evaluation of valvular heart disease for the greater part of the country and partly to the fact that patients with acute myocardial infarction were excluded from the study

There is no significant difference between the

Table II Clinical characteristics of toxic suspected toxic, and nontoxic patients

	Toxic	Suspected toxic	Nontoxic	p value
Number	39	74	536	
Age	60.3 ± 10.9	59.1 ± 11.3	57.5 ± 11.8	NS
Sex male/female	43.6/56.4	52.1/47.9	58.8/41.2	NS
Height (cm)	166.7 ± 9.1	166.3 ± 9.3	168.8 ± 9.1	p <0.04
Weight (kg)	62.9 ± 11.2	64.4 ± 13.0	67.0 ± 12.1	p <0.05
Cardiac diagnosis (%)				
Angina pectoris	10.3	13.5	8.9	NS
Old myocardial infarction	12.8	14.9	18.1	NS
Other coronary heart disease	0.0	1.4	1.1	NS
Valvular heart disease	64.1	45.9	57.4	NS
Cardiomyopathy	7.7	9.5	6.1	NS
Congenital heart disease	2.6	8.1	5.7	NS
Hypertensive heart disease	7.7	12.2	6.3	NS
Cor pulmonale	0.0	1.4	1.7	NS
Other	2.6	5.4	5.0	NS
Previous arrhythmia (%)	90.3	91.3	61.7	p p <0.001
Pneumonia (%)	2.6	4.1	2.8	NS
Bronchial asthma (%)	0.0	2.7	3.0	NS
Emphysema (%)	2.0	8.1	4.4	NS
Chronic nephritis (%)	0.0	5.4	5.0	NS
Nephrosis (%)	0.0	1.4	0.0	NS
Dialysis (%)	0.0	0.0	0.6	NS
Hepatic disease (%)	2.6	1.4	1.3	NS
Malabsorption/ventricular resection (%)	0.0	4.1	2.6	NS
Myxedema (%)	2.6	1.4	0.2	NS
Thyrotoxicosis (%)	0.0	0.0	0.6	
Functional Class N Y H A				
I (%)	13.2 } 42.1	6.3 } 46.0	10.1 } 58.3	
II (%)	28.9	39.7	48.2	p <0.04
III (%)	42.1 } 57.9	36.[illegible] } 54.0	29.8 } 41.7	
IV (%)	15.8	17.[illegible]	11.9	

p p value between toxic and suspected toxic patients
p p value between toxic and nontoxic patients
p p value between suspected toxic and nontoxic patients

etiologic groups with regard to toxicity It is especially worthwhile to note that no patient with cor pulmonale was in the toxic group Neither was there any increased toxicity in other lung diseases (pneumonia bronchial asthma pulmonary emphysema) It is further remarkable that no patient with kidney diseases chronic nephritis, or nephrosis or on hemodialysis was in the *toxic* group This is contrary to what is observed in patients treated with digoxin Neither did patients with liver diseases or malabsorption have higher incidence of toxicity There are few patients with thyroid diseases

Grouping of the patients into the functional Classes I to IV according to the New York Association (N Y H A) shows that more patients have advanced heart failure classified as functional Classes III and IV in the toxic group than in the nontoxic group The difference is statistically significant (p< 0.04)

Other medication interaction Table III shows that diuretics were the drugs most commonly used besides digitalis but there was no significant difference in the use of diuretics or of potassium supplements among the three groups As expected none of the patients in the toxic group was using diphenylhydantoin, as this drug is an inducer of liver enzymes to increase the hepatic metabolism of digitoxin and thus reduce serum digitoxin concentration More patients in the toxic group were taking quinidine but the difference among the three groups was statistically not significant

Extracardiac symptoms As will be seen from Table IV vomiting/diarrhea extreme fatigue/weakness/neuralgia and color vision were the

Table III Other medication in toxic suspected toxic and nontoxic patients

	Toxic	*Suspected toxic*	*Nontoxic*	*p value*
Number	39	4	536	NS
Diuretics (%)	61 5	60 8	56 8	NS
Aldactone (%)	5 1	6 8	3 1	NS
Potassium (%)	12 8	10 8	11 1	NS
Antihypertensives (%)	5 1	6 8	3 9	NS
Diphenylhydantoin (%)	0 0	1 4	1 5	NS
Beta blockers (%)	2 6	6 8	6 6	NS
Quinidine (%)	17.9	10 8	8 5	NS
Procainamide (%)	2 6	2 7	3 1	NS
Psychopharmaca (%)	2 6	1 4	5 2	NS
Sympatheticomimetic drugs (%)	0 0	0 0	0 6	NS
Calcium (%)	0 0	1 4	0 2	NS

Table IV Extracardiac symptoms in toxic suspected toxic and number of toxic patients related to number with symptoms

	Toxic	*Suspected toxic*	*No toxic/ no with symptoms*	*p value*
Number	39	74		
Nausea (%)	5 1	13 5	2/30	NS
Vomiting/diarrhea (%)	15 4	12.2	7/30	NS
Anorexia (%)	20 5	31 1	9/57	NS
Extreme fatigue (%)	10 3	20 3	5/30	NS
Weakness neuralgia (%)	[illegible]7	1 4	3/6	NS
Psychosis/delirium (%)	2 6	0 0	1/2	NS
Color vision (%)	10.3	4 1	4/8	NS
Flickering (%)	7 7	5 4	3/20	NS
Blurred vision (%)	6	4 1	1/6	NS

Table V ECG changes in toxic suspected toxic and number of toxic patients related to number with ECG changes

	Toxic	*Suspected toxic*	*No toxic/ no with ECG changes*	*p value*
Number	39	74		
VPB multifocal (%)	10 3	16 2	4/20	NS
VPB unifocal > 5/min (%)	17 9	20 3	7/28	NS
Bigeminy/trigeminy (%)	10 3	8 1	4/12	NS
Ventricular tachycardia/fibrillation (%)	2 6	2 7	1/6	NS
A T with block (%)	2 6	13 5	1/15	NS
Junctional tachycardia > 80 (%)	5 1	4 1	2/5	NS
Atrial fibrillation/ flutter < 50 (%)	17 9	6 8	7/13	NS
A V block I II and III (%)	25 6	21 6	10/41	NS
S A block junctional rhythm < 50 (%)	5 1	2 7	2/6	NS
Sinus bradycardia (%)	10 3	6 8	4/12	NS
ST T changes (%)	56 4	35 1	23/234	p < 0 02
Ventricular strain (%)	35 9	45 9	1[illegible]/29[illegible]	NS
Old myocardial infarction (%)	10 3	14 9	4/96	NS
QRS prolongation (%)	12 8	9 5	5/49	NS

p p value between toxic and suspected toxic patients

extracardiac symptoms most commonly found in the toxic group These extracardiac symptoms were equally often or more often found in the suspected toxic group with exception of weakness/neuralgia psychosis/delirium color vision and flickering which were most often seen in the toxic group There is however no statistically significant difference in the appearance of these symptoms in toxic and suspected toxic patients As will be seen from Table IV the specificity of these symptoms is not very high Only two of 30 patients with nausea were toxic seven of 30 patients with vomiting/diarrhea nine of 57 patients with anorexia five of 30 patients with extreme fatigue three of 20 patients with flickering and one of six patients with blurred vision The most specific of the extracardiac symptoms were weakness/neuralgia where three of six patients with this symptom were toxic, psychosis/delirium one of two patients color vision four of eight patients As noted these last three symptoms occurred infrequently Altogether 189 extracardiac toxic symptoms were recorded as against 156 cardiac signs of toxicity

ECG signs of toxicity With regard to these cardiac signs of toxicity they occurred as frequently or more frequently in the suspected toxic as in the toxic group (Table V) It is especially worthwhile to note that atrial tachycardia with block was more frequently seen in the suspected toxic than in the toxic group Only

Table VI Biochemical data in toxic, suspected toxic and nontoxic patients

	Toxic	*Suspected toxic*	*Nontoxic*	*p value*
Number	39	74	536	
Hemoglobin	14.4 ± 1.5	14.1 ± 1.8	14.4 ± 1.9	NS
Serum sodium	138.9 ± 3.6	138.6 ± 5.5	139.4 ± 3.6	NS
Serum potassium	4.2 ± 0.5	4.3 ± 0.6	4.4 ± 0.5	NS
Serum chloride	99.4 ± 4.3	99.2 ± 4.5	100.5 ± 0.4	p < 0.02
Serum magnesium	1.5 ± 0.1	1.6 ± 0.2	1.6 ± 0.2	p < 0.002
				p < 0.006
Serum calcium	4.7 ± 0.2	4.7 ± 0.3	4.7 ± 0.3	NS
Serum phosphate	2.9 ± 0.7	3.5 ± 0.7	3.1 ± 0.7	p < 0.0005
				p* < 0.0005
Total protein	6.9 ± 0.0	6.9 ± 0.5	6.9 ± 0.5	NS
Serum albumin	4.0 ± 0.6	3.7 ± 0.7	3.8 ± 0.7	NS
Blood urea	38.4 ± 13.8	47.2 ± 36.2	41.5 ± 27.3	NS
Serum creatinine	1.0 ± 0.2	1.2 ± 0.7	1.1 ± 0.8	NS
Serum bilirubin	0.8 ± 0.3	1.0 ± 0.8	0.9 ± 0.5	p < 0.05
				p < 0.05
Arterial pH	7.43 ± 0.04	7.42 ± 0.05	7.42 ± 0.04	NS
Arterial P_{CO}	38.0 ± 4.0	39.6 ± 5.0	40.1 ± 5.5	NS
Standard bicarbonate	26.0 ± 2.5	25.7 ± 2.9	25.5 ± 2.4	NS
Proteinuria (%)	13.2	20.0	14.8	NS
Protein bound iodine	5.0 ± 1.1	5.2 ± 1.5	6.3 ± 1.7	p* < 0.04

p p value between toxic and suspected toxic patients
p p value between toxic and nontoxic patients
p p value between suspected toxic and nontoxic patients

atrial fibrillation/flutter with a ventricular rate below 50 sinoatrial block with junctional rhythm below 50 and sinus bradycardia were more commonly seen in the toxic than in the nontoxic group

With regard to the specificity of these cardiac signs of toxicity it was also low as it was for the extracardiac signs Only four of 20 patients with ventricular multifocal extrasystoles were toxic seven of 28 patients with ventricular extrasystoles more than 5 per minute four of 12 patients with bigeminy or trigeminy and one of six patients with ventricular tachycardia or fibrillation Only one of 15 patients with atrial tachycardia with block was toxic two of five patients with junctional tachycardia seven of 13 patients with atrial flutter or fibrillation with a ventricular rate below 50 10 of 41 patients with A V block two of six patients with S A block with junctional rhythm below 50 and four of 12 patients with sinus bradycardia In this study thus junctional tachycardia, atrial fibrillation or flutter with a ventricular rate below 50, and S A block with junctional rhythm below 50 were the most specific ECG signs of toxicity With regard to other ECG signs, ST T changes and QRS prolongation were more often seen in the toxic group whereas ventricular strain and old myocardial infarction were more commonly seen in the suspected toxic group There was however, no statistical difference in the appearance of these signs apart from ST changes ($p < 0.02$)

Biochemical data Of the biochemical data listed in Table VI only hypomagnesemia was significantly more common in the toxic than in the nontoxic group ($p < 0.002$) Serum chloride was significantly lower in the suspected toxic than in the nontoxic group ($p < 0.02$) Serum phosphate was significantly lower in the toxic than in the suspected toxic group ($p < 0.0005$) and it was also lower in the nontoxic group than in the suspected toxic group ($p < 0.0005$) but there was no statistically significant difference between the toxic and nontoxic groups Likewise serum bilirubin was significantly lower in the toxic than in the suspected toxic group ($p < 0.05$) and it was also lower in the nontoxic than in the suspected toxic group ($p < 0.05$) There was no significant difference between the toxic and nontoxic groups Protein bound iodine was significantly lower in the suspected toxic than in the nontoxic group ($p < 0.04$), whereas there was no significant differ

Table VII Digitoxin dosage and serum concentration in toxic suspected toxic and nontoxic patients

	Toxic	*Suspected toxic*	*Nontoxic*	*p value*
Number	39	74	536	
Digitoxin dosage (mg)	0 096 ± 0 042	0 085 ± 0 0[illegible]5	0 081 ± 0 0[illegible]1	p < 0 005 p < 0 03
Digitoxin concentration (ng /ml)	27 6 ± 12 1	15 7 ± 6 8	16 0 ± 7.2	p < 0 0001 p < 0 0001

p p alue between t xic and su pected t xic groups
p p l e between t xic and nontoxic patients.

ence between the toxic and nontoxic groups Determination of protein bound iodine was however done in only 77 of the patients

Digitoxin dosage and serum concentrations The dosage of digitoxin (Table VII) was significantly higher in the toxic than in the nontoxic group (p< 0 05) and in the toxic than in the suspected toxic group (p< 0 03) whereas there was no significant difference between the suspected toxic and the nontoxic groups As expected serum digitoxin concentration was significantly higher in the toxic than in the nontoxic group (27 6 ± 12 1 vs 16 0 ± 7 2) (p< 0 0001) It was also significantly higher in the toxic than in the suspected toxic group (p< 0 0001) Serum digitoxin concentration was almost the same in the suspected toxic (15 7 ± 6 8 ng per milliliter) as in the nontoxic group (16 0 ± 7 2 ng per milliliter)

A comparison between patients in functional Classes I and II with those in Classes III and IV shows that the dose of digitoxin is not significantly different Nor is there any significant difference between serum digitoxin concentration in these groups (Table VIII)

Table VIII Digitoxin dosage and serum concentration in functional Classes I and II compared to functional Classes III and IV

	Functional Classes I and II	*Functional Classes III and IV*
Number	346	303
Digitoxin dosage (mg)	0 081 ± 0 023	0 085 ± 0 023
Digitoxin concentration (ng /mL)	17 0 ± 8.5	16 2 ± 7 4

Discussion

Incidence of digitalis toxicity The most remarkable finding in this study is the low incidence of digitalis toxicity in 649 patients on maintenance treatment with digitoxin The incidence of toxicity of 5 8 per cent is far lower than in the previously reported prospective studies on digitalis intoxication where the incidence of toxicity ranged from 15 to 23 per cent We feel that this is not due to the glycoside used as Beller and associates found no difference in incidence of digitalis toxicity between patients using digitoxin or digoxin However only nine patients using digitoxin were included in that study We think the main reason is that digitalis is used in lower doses than previously recommended The mean maintenance dose in our study was 0 096 in the toxic group 0 085 in the suspected toxic group and 0 081 in the nontoxic group In the study of Beller and associates the mean maintenance dose of digitoxin was 0 10 mg in the toxic and 0 11 mg in the nontoxic group This is also reflected in the serum concentration as altogether 307 patients had a serum digitoxin concentration below 15 ng per milliliter 271 patients between 15 and 25 ng per milliliter and only 71 had a concentration above 25 ng per milliliter The use of serum concentration determination of digitalis glycosides may also alert the clinician to a more individualized digitalis dosage regimen[7]

The exclusion of patients with acute myocardial infarction cannot explain the low prevalence of digitalis toxicity in this study Such patients were included in the study of Beller and associates who found no difference in the prevalence of previous or acute myocardial infarction between toxic and nontoxic patients

The recommendation for clinical use of digitoxin in this country has for many years been that patients who are not in need of immediate digitalization should receive a dose of 0 6 mg of digitoxin for 2 days and thereafter 0 1 mg a day

Patients with supraventricular tachycardia and in frank congestive heart failure have been recommended intravenous digitalization with a rapidly acting glycoside, mostly Deslanoside 1 2 mg intravenously and immediately started on a maintenance dose of 0 1 mg of digitoxin a day Further it has been recommended to decrease the dose in patients above 60 years and in patients with weight below 60 kilograms Thus a maintenance dose of 0 1 mg 5 days a week is very usual in elderly or thin individuals It has further been recommended to increase the dose in thyrotoxic individuals and to decrease the dose in patients with myxedema

Renal function The other important finding in this study is the absence of digitalis toxicity in patients with renal failure This is contrary to the findings in studies of patients using digoxin where there is an increased incidence of toxicity in those with reduced renal function[1,4,9] Digoxin is mainly excreted unchanged through the kidneys and there is a rough correlation between serum digoxin concentration and creatinine clearance with a correlation coefficient of 0 8 to 0 9[1,11] Digitoxin on the other hand is extensively metabolized in the liver and partly excreted as metabolites The elimination of digitoxin is therefore independent of kidney function[1] This is also confirmed by the present study as none of the patients with digitalis toxicity had reduced renal function Patients with kidney diseases also have lower serum digitoxin concentration than other patients on the same dose[11]

Age and weight Contrary to the findings in some studies of digoxin intoxication[3,4,9] there was in the present study no significant influence of age on the incidence of toxicity The usual explanation for the finding of a higher incidence of toxicity in older patients using digoxin is the reduced renal clearance observed in individuals over 60 years of age In patients using digitoxin the elimination of the drug is independent of renal function and should thus not be dependent on age The absence of increased toxicity in the older age group might also be explained by the recommendation to reduce digitoxin dosage in elderly individuals

There is an increased incidence of toxicity in patients with low body weight and this strengthens our recommendation of reducing digitalis dosage in thin individuals Studies with digoxin have, on the other hand, shown no influence of body weight on incidence of toxicity[4] In the study of Shapiro and associates body weight was even higher in toxic than nontoxic patients

Heart diseases Supporting the findings of Beller and associates,[1] we observed no increased incidence of digitalis toxicity in patients with arteriosclerotic heart disease

There was also no increased incidence of digitalis toxicity in patients with cardiomyopathy confirming the findings of Killip and associates[14]

Other diseases It is further worthwhile to note that patients with lung disease do not have an increased incidence of digitalis toxicity as found in other studies[1,15,16]

As digitalis is metabolized in the liver one should expect patients with reduced liver function to have an increased incidence of digitalis toxicity As we have seen there is no increased toxicity in these patients but only a few patients with liver diseases are included in this study Recent studies on the influence of reduced liver function on the pharmacodynamics of digitoxin have shown that digitoxin is eliminated more rapidly in patients with chronic active hepatitis[17]

Functional class There are distinctly more toxic patients in functional Classes III and IV than in those with less advanced heart failure The same observation has been made by Beller and associates[1] The explanation for this finding is not obvious It might reflect a reduced liver function in patients with advanced congestive heart failure, as suggested by Beller and associates,[1] who found higher bilirubin and SGOT and lower serum albumin in toxic patients In our study there was no significant difference in these biochemical data between toxic and nontoxic patients The increased toxicity is not due to higher serum concentrations and thus might reflect a decreased tolerance to digitalis in patients with advanced congestive heart failure It was not due to higher dosage of digitoxin in patients in functional Classes III and IV

Diuretics Contrary to previous findings, there was no increased use of diuretics in patients with digitalis toxicity Likewise there was no significant hypopotassemia in the toxic group, as has been observed in some other studies[2,18,19]

The influence of diuretics may however, be reflected in a lower serum magnesium concentration in the toxic than in the nontoxic group The

low magnesium concentration may also be caused by a low food intake caused by anorexia The finding of reduced magnesium concentration in patients with digitalis toxicity has been observed by Seller and associates [2]

Diagnosis of digitalis intoxication Digitalis toxicity is usually diagnosed from extracardiac signs from the gastrointestional tract from the nervous system and from ECG signs In this study there was an increased incidence of vomiting/diarrhea muscular weakness/neuralgia and color vision in the toxic group although the difference was not statistically significant The specificity of these extracardiac signs was low Anorexia and vomiting/diarrhea were unspecific signs Muscular weakness/neuralgia and color vision were more specific as half of the patients exhibiting these signs were toxic These signs were however infrequently found altogether in only 14 patients among the 649 patients studied

Multifocal ventricular extrasystoles unifocal ventricular extrasystoles more than five per minute bigeminy or trigeminy junctional tachycardia with a ventricular rate above 80 atrial fibrillation or flutter with a ventricular rate below 50 and A V block S A block with junctional rhythm below 50 and sinus bradycardia were more commonly found in the toxic than in the suspected toxic or nontoxic group These ECG signs were not very specific as previously observed by Surawicz and Mortelmans who found that only 10 of 30 patients exhibiting these signs were toxic The most specific ECG signs in this study were junctional tachycardia with a ventricular rate above 80 atrial fibrillation or flutter with a ventricular rate below 50 and S A block with junctional rhythm below 50 As emphasized by Chung and by Beller and associates supraventricular rhythm disturbances were more commonly seen in digitalis intoxication than ventricular arrhythmias

Determination of serum digitoxin concentration seems to be a reliable guide to the diagnosis of digitoxin toxicity The serum concentration in the toxic patients was significantly higher than in the nontoxic group where it was the same as in the suspected toxic group Fig 1 shows that there is no sharp distinction between serum concentration in the toxic and nontoxic and suspected toxic groups There is some overlapping as patients with digitalis toxicity might have serum concen

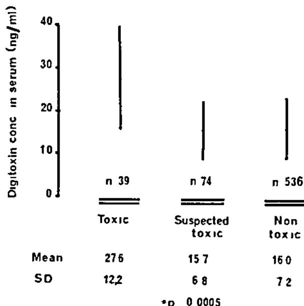


Fig 1 Serum digitoxin concentration in toxic suspected toxic and nontoxic patients (mean ± S D)

tration below 25 ng per milliliter in the range usually considered as being therapeutic On the other hand it is worth noting that 49 of the nontoxic patients had a serum digitoxin concentration above 25 ng per milliliter

The value of serum digitoxin determination In this study the diagnosis of digitalis intoxication was made on clinical grounds Intoxication was diagnosed when extracardiac or cardiac signs or symptoms of digitalis toxicity disappeared in 6 (10) days following withdrawal of digitoxin Digitoxin serum levels in the toxic patients on admission varied greatly from 7 5 to 56 ng per milliliter Six toxic patients had digitoxin concentration below 15 ng per milliliter 11 between 15 and 25 ng per milliliter which is considered to be the therapeutic range and 22 a concentration above 25 ng per milliliter Patients with a low digitoxin concentration had few symptoms of digitalis intoxication Only one patient had extracardiac symptoms whereas all six had one or two ECG signs mostly ventricular extrasystoles The patient with the lowest concentration of 7 5 ng per milliliter had only ventricular extrasystoles more than five per minute This illustrates the difficulty in establishing valid criteria for the diagnosis of digitalis intoxication

It is well known from other studies that there may be considerable overlap in serum digitoxin concentration between toxic and nontoxic pa

Patients with supraventricular tachycardia and in frank congestive heart failure have been recommended intravenous digitalization with a rapidly acting glycoside, mostly Deslanoside 1.2 mg intravenously, and immediately started on a maintenance dose of 0.1 mg of digitoxin a day. Further it has been recommended to decrease the dose in patients above 60 years and in patients with weight below 60 kilograms. Thus a maintenance dose of 0.1 mg 5 days a week is very usual in elderly or thin individuals. It has further been recommended to increase the dose in thyrotoxic individuals and to decrease the dose in patients with myxedema.

Renal function. The other important finding in this study is the absence of digitalis toxicity in patients with renal failure. This is contrary to the findings in studies of patients using digoxin where there is an increased incidence of toxicity in those with reduced renal function.[1, 4, 8] Digoxin is mainly excreted unchanged through the kidneys and there is a rough correlation between serum digoxin concentration and creatinine clearance with a correlation coefficient of 0.8 to 0.9.[10, 11] Digitoxin on the other hand is extensively metabolized in the liver and partly excreted as metabolites. The elimination of digitoxin is therefore independent of kidney function.[1] This is also confirmed by the present study as none of the patients with digitalis toxicity had reduced renal function. Patients with kidney diseases also have lower serum digitoxin concentration than other patients on the same dose.[1]

Age and weight. Contrary to the findings in some studies of digoxin intoxication[3, 4, 8] there was in the present study no significant influence of age on the incidence of toxicity. The usual explanation for the finding of a higher incidence of toxicity in older patients using digoxin is the reduced renal clearance observed in individuals over 60 years of age. In patients using digitoxin the elimination of the drug is independent of renal function and should thus not be dependent on age. The absence of increased toxicity in the older age group might also be explained by the recommendation to reduce digitoxin dosage in elderly individuals.

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As digitalis is metabolized in the liver one should expect patients with reduced liver function to have an increased incidence of digitalis toxicity. As we have seen there is no increased toxicity in these patients but only a few patients with liver diseases are included in this study. Recent studies on the influence of reduced liver function on the pharmacodynamics of digitoxin have shown that digitoxin is eliminated more rapidly in patients with chronic active hepatitis.[17]

Functional class. There are distinctly more toxic patients in functional Classes III and IV than in those with less advanced heart failure. The same observation has been made by Beller and associates.[1] The explanation for this finding is not obvious. It might reflect a reduced liver function in patients with advanced congestive heart failure, as suggested by Beller and associates[1] who found higher bilirubin and SGOT and lower serum albumin in toxic patients. In our study there was no significant difference in these biochemical data between toxic and nontoxic patients. The increased toxicity is not due to higher serum concentrations and thus might reflect a decreased tolerance to digitalis in patients with advanced congestive heart failure. It was not due to higher dosage of digitoxin in patients in functional Classes III and IV.

Diuretics. Contrary to previous findings there was no increased use of diuretics in patients with digitalis toxicity. Likewise there was no significant hypopotassemia in the toxic group as has been observed in some other studies.[2, 3, 19]

The influence of diuretics may, however, be reflected in a lower serum magnesium concentration in the toxic than in the nontoxic group. The

REFERENCES

1 Beller G A Smith T W Abelmann W H Haber E., and Hood W B Jr Digitalis intoxication A prospective clinical study with serum level correlations, N Engl J Med 284 989 1971
2 Shapiro S Slone D Lewis, G P and Jick H The epidemiology of digoxin, J Chron Dis 22 361 1969
3 Hurwitz N and Wade O L. Intensive hospital monitoring of adverse reactions to drugs Br Med J 1 531 1969
4 Evered D C and Chapman C Plasma digoxin concentrations and digoxin toxicity in hospital patients Br Heart J 33 540 1971
5 Howard D Smith, C I Stewart G Vadas M Tiller D J Hensley W J and Richards J G A prospective survey of the incidence of cardiac intoxication with digitalis in patients being admitted to hospital and correlation with serum digoxin levels N Z Med J 3 279 1973
6 Gjerdrum K Determination of digitalis in blood Acta Med Scand 187 371 1970
7 Koch Weser J Duhme D W and Greenblatt D J Influence of serum digoxin concentration measurements on frequency of digitoxicity Clin Pharmacol Ther 16 284 1974
8 Duhme D W Greenblatt D J and Koch Weser J Reduction of digoxin toxicity associated with measurement of serum levels Ann Intern Med 80 516 1974
9 Smith, T W and Haber E Digoxin intoxication The relationship of clinical presentation to serum digoxin concentration J Clin Invest 49 2377 1970
10 Doherty J E The influence of renal function on digoxin metabolism in Storstein O editor Symposium on digitalis Oslo 1973 Gyldendal Norsk Forlag p 168
11 Falch, D and Teien A The influence of kidney function on the plasma level and urinary excretion of digoxin in Storstein O editor Symposium on digitalis Oslo 1973 Glydendal Norsk Forlag p 183
12 Storstein L Studies on digitalis I Renal excretion of digitoxin and its cardioactive metabolites Clin Pharmacol Ther 16 25 1974
13 Rasmussen K Jervell J Storstein L and Gjerdrum K Digitoxin kinetics in patients with impaired renal function Clin Pharmacol Ther 13 6 1972
14 Kilip T Donnelly W and Morrison J Digitalis and cardiomyopathy Circulation 46 (suppl II) 46 1972
15 Baum G L Dick, M M and Blum A Factors involved in digitalis sensitivity in chronic pulmonary insufficiency Am Heart J 57 460 1959
16 Hargreave F E Digitalis and cor pulmonale Br Med J 2 943 1965
17 Storstein L and Amlie J Digitoxin pharmacokinetics in chronic active hepatitis, Digestion 12 353 1975
18 Jorgensen A W and Sorensen O H Digitalis intoxication Acta Med Scand 188 179 1970
19 Steiness E Incidence of electrolyte disturbances on the effect of digitalis Acta Cardiol Suppl 17 145 1973
20 Seller R H Cangiano J Kim K E Mendelssohn S Brest A N and Swartz C Digitalis toxicity and hypomagnesemia Am Heart J 79 57 1970
21 Surawicz B and Mortelmans, S Factors affecting individual tolerance to digitalis in Fisch S and Surawicz B Editors Digitalis New York 1969 Grune & Stratton Inc p 127
22 Chung E K Digitalis intoxication Amsterdam 1969 Excerpta Medica Foundation
23 Klein M D Lown B Barr I Hagemeijer F., Garrison H and Axelrod P Comparison of serum digoxin level measurement with acetyl strophantidin tolerance testing Circulation 49 1053 1974
24 Storstein L. The ratio between myocardial and serum levels of digitoxin in Storstein O editor Symposium on digitalis Oslo 1973 Gyldendal Norsk Forlag P 249
25 Chamberlain D A The ratio between myocardial and plasma levels of digoxin in Storstein O editor Symposium on digitalis Oslo 1973 Gyldendal Norsk Forlag p 262
26 Redfors A., Bertler A and Schuller H The ratio between myocardial and plasma levels of digoxin in man in Storstein O editor Symposium on digitalis Oslo 1973 Gyldendal Norsk Forlag p 265
27 Güllner H G Stinson E B Harrison D C and Kalman S M Correlation of serum concentrations with heart concentrations of digoxin in human subjects Circulation 50 653 1974
28 Solomon H M and Abrams W B Interactions between digitoxin and other drugs in man Am Heart J 83 277 1972
29 Storstein L Studies on digitalis VII The influence of nephrotic syndrome on protein binding pharmacokinetics and renal excretion of digitoxin and cardioactive metabolites Clin Pharmacol Ther (In press)
30 Storstein L. The influence of renal function on the pharmacokinetics of digitoxin in Storstein O editor Symposium on digitalis Oslo 1973 Gyldendal Norsk Forlag p 158
31 Storstein O Digitoxin present knowledge of pharmacokinetics and pharmacodynamics in Storstein O editor Symposium on digitalis Oslo 1973 Gyldendal Norsk Forlag p 410

tients A study of the relation between serum digoxin level and a tolerance test to acetylstrophanthidin in 133 patients by Klein and associates,[3] showed that there were discordant results between these estimations in 42 per cent of the tests

One reason for discrepancy between clinical diagnosis of digitalis intoxication and serum glycoside determinations may be a discrepancy between serum and myocardial concentrations of digitalis glycosides A study of digitoxin[4] showed a wide range in myocardial/serum ratios of digitoxin This study also showed that the metabolic pattern of digitoxin in myocardium differs from that in serum

Most studies of digoxin also show a wide range in myocardial/serum ratios,[5, 6] whereas the study by Gullner and associates showed a remarkable constant ratio between myocardial and serum concentrations of digoxin (23 9 ± 3 2) A number of factors may influence the response of the diseased human myocardium to digitalis glycosides

Determination of digitalis serum levels is thus a guide to the diagnosis of digitalis intoxication but the diagnosis should still be based on clinical grounds by observing the response of digitoxin withdrawal in patients exhibiting symptoms or signs of intoxication

Apart from being a guide to digitalis toxicity, serum determination of digitalis glycosides may also be a guide to underdigitalization Especially in patients in sinus rhythm it is difficult to judge the adequacy of digitalization on clinical grounds Digitalis serum concentration will be a guide to the correct level of digitalization We have used digitoxin in lower doses than previously recommended and find that altogether 307 patients had serum digitoxin levels below 15 ng per milliliter which is considered to be in the lower therapeutic range The finding of low serum digitalis concentrations should be an indication to increase the doses under clinical supervision Some patients may however, be adequately digitalized in spite of low serum concentrations We know that patients taking drugs which interact with liver enzymes to increase the hepatic metabolism of digitoxin like diphenylhydantoin and barbiturates in daily doses of 0 2 Gm or more have low digitoxin levels Patients with nephrotic syndrome[9] and patients on treatment with hemodialysis[10] should be kept on lower levels whereas other patients with impaired renal function can be treated with the usual doses of digitoxin Further patients with sick sinus syndrome tolerate small doses of digitalis and should therefore be kept on low serum levels of digitoxin[11]

Summary

In a prospective study of digitalis intoxication in 649 patients on maintenance treatment with digitoxin a low incidence of digitalis toxicity was found, namely, 5 8 per cent This is mainly due to a more careful use of digitalis glycosides It is especially important to reduce the dose of digitoxin in elderly and thin individuals Digitoxin is metabolized in the liver and partly excreted through the kidneys as metabolites Serum half time of digitoxin is shortened in patients with impaired renal function Patients with reduced renal function may be treated with digitoxin in the same doses as individuals with normal renal function This is in contrast to patients treated with digoxin Digitoxin should therefore be the cardiac glycoside of choice in treatment of patients with renal failure Digitoxin is further rapidly eliminated in patients with reduced liver function in spite of its extensive hepatic metabolism

In this study extracardiac symptoms were found equally often as cardiac signs of toxicity Patients intoxicated usually had several symptoms and signs of toxicity at the same time The specificity of commonly used symptoms and signs of digitalis intoxication is very low In this study atrial tachycardia with block which has been considered to be an important cardiotoxic arrhythmia very seldom was found in digitalis intoxication

There is an overlap in digitalis serum concentration between toxic and nontoxic patients The diagnosis of toxicity was made on clinical grounds Most of the intoxicated patients had high serum concentrations but some had concentrations in the normal or low range Apart from being a guide to the diagnosis of digitalis intoxication serum digitalis levels may further be a guide to underdigitalization of cardiac patients especially patients in sinus rhythm

We thank Anne Thune Larsen for expert technical assistance Hans Kristian Langva for computer and statistical assistance and the Departments of Clinical Chemistry for most of the biochemical data given in Table VI

month treatment phase the remaining 22 patients received vitamin E during the second 6 month treatment phase The mean duration of double blind therapy was 189 ± 15 0 days of vitamin E and 192 ± 13 3 days of placebo In addition all patients received 2 months of placebo therapy known only to the cardiologist (single blind during which time patients continued to keep diaries) following each 6 month double blind treatment phase

Vitamin E in the form of *d* alpha tocopherol succinate 400 I U per capsule and a placebo capsule containing 2 5 mg of riboflavin (for purposes of a urine fluorescence test to judge drug adherence) were prescribed four times daily during the study This dosage of vitamin E has been reported effective in angina by Shute Analysis by an independent laboratory found 397 9 I U of *d* alpha tocopheryl acid succinate in randomly selected capsules that were claimed by the manufacturer to contain 400 I U No antianginal agents other than nitroglycerin were taken by the subjects for the duration of the study Patients were advised to continue the same habits of physical activity diet and smoking throughout the study Patients avoided the use of multivitamins as well as mineral oil and iron preparations which may interfere with absorption of vitamin E Three patients who were taking wheat germ (two patients) or vitamin E (one patient) previously had not taken any form of vitamin E therapy for at least 2 months before entering this study Although the lack of toxic effects from large doses of vitamin E has been emphasized all patients participating in this project were questioned at each visit for possible side effects and all received periodically a complete blood count urinalysis blood chemistries (urea nitrogen sugar bilirubin uric acid calcium phosphorus lactic dehydrogenase transaminase albumin and cholesterol) prothrombin time chest x ray and ECG Drug adherence was followed by capsule count and a urine fluorescence test that was performed by a technician who reported the fluorescence results to the investigators only at the completion of the project in order that the study might remain blind to the investigators Serum vitamin E levels determined by gas liquid chromatography which were measured at baseline and at the end of the first and sixth months of each treatment phase were also not made available to the project cardiologist until completion of the study

All patients were seen in the Cardiology Clinic at least once monthly by the same cardiologist who was always unaware of whether the patients were receiving vitamin E or placebo During each visit the cardiologist made a careful review of the patient s daily angina diary and obtained the patient s impression of his ability to perform his daily activities Thus the symptomatic effects of treatment were measured by both carefully recording of angina attacks and the number of nitroglycerin tablets used

The effects of treatment were measured quantitatively both by systolic time interval assessment of left ventricular function according to the method of Weissler and by the multistage maximal exercise treadmill test designed by McDonough and Bruce [7] All patients were studied in a fasting state (including abstinence from tobacco) between the hours of 8 A M and 12 noon Systolic time intervals were measured on a DR 8 Electronics for Medicine Research Recorder with 200 mm per second photographic paper speed and 20 msec time lines with simultaneous recording of the ECG phonocardiogram and carotid arterial pulse QS (total electromechanical systole) LVET (left ventricular ejection time) PEP (pre ejection phase) and PEP/LVET were determined on 10 consecutive beats in subjects who had rested supine for at least 10 minutes prior to the exercise test Systolic time interval indices (QS I LVETI and PEPI) were derived from the measured intervals by applying the regression equations of Weissler Patients walked on the treadmill with ECG (lead CB) and cuff blood pressure monitoring and recording until they developed angina pectoris Duration of exercise on the treadmill degree of ST depression on the ECG product of maximum heart rate times maximum systolic blood pressure and degree of functional aerobic impairment were assessed from performance on the treadmill Functional aerobic impairment was derived from duration on the treadmill by use of a nomogram which adjusts for age sex and habitual physical activity Each patient during the study had a total of six systolic time interval measurements and six maximal treadmill tests (two at baseline and two at the end of each of the two double blind treatment phases) The data from each two

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Quantitative evaluation of vitamin E in the treatment of angina pectoris

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Vitamin E has been the subject of numerous scientific reports, but there still remains uncertainty as to its usefulness in the treatment of disease states in man.[1] Perhaps the most controversial issue is whether or not vitamin E is beneficial for patients with cardiovascular disease. Large doses of vitamin E for angina pectoris have been repeatedly reported since 1946 to be effective therapy for angina pectoris by Shute and Vogelsang, by Toone in 1973, and as possibly effective by Anderson in 1974. Vitamin E therapy for patients with angina failed to find general acceptance after negative reports appeared in the earlier medical literature; however, there is both laboratory and clinical evidence to suggest that vitamin E has several actions which could be of therapeutic benefit to such patients. It has been reported that experimental animals fed vitamin E are better able to survive anoxic conditions than nontreated litter mates; that animals receiving vitamin E have reduced basal oxygen consumption (suggesting better utilization of oxygen by tissue); that in experimental myocardial infarction in dogs vitamin E increases the collateral blood supply and decreases fibrosis in the infarcted area; that vitamin E has a mild anticoagulant and fibrinolytic effect, and that vitamin E improves intermittent claudication in patients with femoropopliteal occlusion and poor distal arteries.

Prior studies of vitamin E in angina pectoris patients were performed without the new technical methods, which both make possible a high degree of diagnostic accuracy in selecting patients for study with angina pectoris and also provide improved means of quantitating response to therapy. The present study utilized currently available quantitative methods of cardiac evaluation to determine whether or not a large dose (1600 I.U. daily of *d*-alpha tocopherol) of vitamin E produced any measurable improvement in 48 patients with established angina pectoris plus obstructive coronary disease.

Methods

Fifty-two patients (mean age 57 years) who were considered by two cardiologists to have typical, stable effort-related angina pectoris gave verbal and written (signed) informed consent to participate in a double-blind cross-over study of 6 months of vitamin E therapy vs. 6 months of placebo therapy. All patients had Q wave electrocardiographic (ECG) evidence of previous myocardial infarction as defined by the Minnesota criteria (25 patients) and/or positive coronary arteriograms as defined by 75 per cent obstruction of at least one major coronary artery (31 patients). Each patient demonstrated reproducible ischemic ECG changes of 1 mm. or more flat or down-sloping ST segment depression below the PR segment associated with characteristic chest pain on maximal exercise treadmill testing. Since four patients died during the course of the study, 48 patients completed the project. Twenty-six patients received vitamin E during the first 6

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frequency during placebo. Comparison of the 2 month single blind placebo phases which followed each 6 month double blind treatment phase failed to show any significant difference in the frequency of angina or nitroglycerin consumption. The lack of increase in frequency of chest pain or nitroglycerin consumption during the 2 months (single blind) after vitamin E therapy appears to exclude acceleration of angina due to withdrawal of vitamin E. Thus the daily angina diaries fail to give any quantitative evidence of relief of angina pectoris during the 6 months of vitamin E therapy.

Another means used to evaluate response of these angina patients to vitamin E therapy was to determine whether or not patients showing improvement in angina by one method of testing (e.g., the exercise test) showed *concurrent* improvement in the other measured parameters (i.e., angina diary record and systolic time interval measurements). There were eight of the 48 patients (17 per cent) showing any degree of improvement (over both baseline and placebo phase) in functional aerobic impairment as measured by the exercise tests who at the same time showed even the slightest reduction in chest pain frequency while taking vitamin E therapy. Of these eight patients only four also showed improvement in PEP/LVET. On the other hand, six of 48 patients (12 per cent) showed improvement of functional aerobic impairment and reduction in frequency of angina while on placebo therapy. Three of these individuals also improved PEP/LVET during placebo therapy. Therefore four of 48 (8 per cent) of the patients in this study showed simultaneous improvement in all the quantitative measurements for angina during vitamin E therapy, whereas three of 48 (6 per cent) patients responded in a similar fashion to placebo. The small difference in improvement in the two treatment groups was not statistically significant ($\chi^2 = 0$). It is concluded that vitamin E failed to produce consistent measureable improvement in the parameters studied in even a few of the 48 patients.

There were four deaths during the project, two of which occurred suddenly at home (apparently cardiac deaths) and two of which occurred during hospitalization for recurrent myocardial infarction (established at autopsy). Two deaths occurred in patients receiving vitamin E and the other two occurred in patients receiving placebo therapy. There were 11 episodes requiring admission to the hospital during the course of the study because of acute myocardial infarction (three patients) or the development of unstable angina pectoris (eight patients). Five of these admissions occurred during the period of vitamin E therapy and six occurred during the placebo therapy. Patients with unstable angina pectoris or myocardial infarction continued to receive vitamin E or placebo during hospitalization according to the double blind cross over design of the study and were included in the statistical analysis of the results. This study produces no evidence that 1600 I.U. of vitamin E daily is of value in reducing morbid events in patients with angina pectoris.

Table III Daily angina diary data 48 patients*

	Angina pains (per week)	*Nitroglycerin (per week)*
Double blind placebo phase (6 months)	6.7 ± 10.5	7.7 ± 14.2
Double blind vitamin E phase (6 months)	7.3 ± 12.6	7.6 ± 12.1
p Value (2 double blind phases)	> 0.80	> 0.95
Single blind placebo phase (2 months after placebo phase)	7.0 ± 10.9	8.1 ± 14.8
Single blind placebo phase (2 months after vitamin E phase)	7.3 ± 14.8	8.0 ± 13.7
p Value (2 single blind phases)	> 0.90	> 0.95

*Mean values ± 1 S.D.

Analysis of the drug adherence data shows that these patients were reliable in taking the medication. The capsule count data shows a mean consumption of 88 per cent of the prescribed capsules during vitamin E phase and 84 per cent consumption during placebo therapy. The urine fluorescence test which was used to evaluate capsule consumption during placebo therapy proved to be a somewhat less reliable method of following drug consumption since the technician judged a significant number of urine specimens as showing an equivocal response. Even if the equivocal responses are considered negative, the per cent of urine specimens with fluorescence indicate that these patients were taking the prescribed placebo medication at least 78 per cent of the time. The serum tocopherol levels measured in 46 patients showed a mean level of 0.77 ± 0.90 mg per 100 ml at baseline in comparison to

Table I Serial maximum exercise treadmill tests in 48 patients*

Test state	*Duration on treadmill (min)*	*Functional aerobic impairment (%)*	*Max HR × SBP / 100*	*ST depression (mm)*
Baseline	5.33 ± 1.59	24.6 ± 19.3	231 ± 48.8	2.3 ± 1.38
Placebo phase	5.30 ± 1.60	23.8 ± 18.8	224 ± 44.5	2.4 ± 1.34
Vitamin E phase	5.48 ± 1.69	22.5 ± 18.8	229 ± 48.4	2.4 ± 1.45
p Value (vitamin E vs placebo)	> 0.50	> 0.70	> 0.95	> 0.99
p Value (vitamin E vs baseline)	> 0.70	> 0.50	> 0.97	> 0.99

Key mean values ± 1 SD max HR × SBP = maximum heart rate times systolic blood pressure

Table II Systolic time interval measurements in 48 patients*

	PEP/LVET	*QS I*	*LVETI*	*PEPI*
Placebo phase	0.420 ± 0.088	549 ± 18.3	402 ± 20.0	147 ± 16.9
Vitamin E phase	0.416 ± 0.078	550 ± 18.7	405 ± 18.7	145 ± 14.5
p Value	> 0.95	> 0.70	> 0.40	> 0.60

Mean values ± 1 SD

tests were averaged and tabulated at the end of each treatment phase to allow a quantitative determination of the response to therapy

Results

Table I summarizes the results of the maximal exercise treadmill tests at baseline after 6 months of placebo and after 6 months of vitamin E Although the mean duration of exercise on the treadmill during the vitamin E phase (5.48 ± 1.69 min) was slightly better than during baseline (5.33 ± 1.59 min) or placebo phase (5.30 ± 1.60 min) the difference was too small to be statistically significant The small differences in duration of exercise are well within the expected 10 per cent variation that defines the limits of reproducibility of this test The per cent functional aerobic impairment an index of the ability of the cardiovascular system to satisfy the aerobic requirements of the body, showed virtually no change during the 6 months of vitamin E and did not approach the 13 per cent reduction required for significant improvement beyond that due to test variation [6] The double product (maximum heart rate times systolic blood pressure/100) which is a parameter of myocardial oxygen consumption, failed to show a significant increase on vitamin E therapy as would be expected if myocardial perfusion improved A further index of myocardial ischemia is the degree of ST depression occurring with exercise ECG No significant decrease in the amount of ST depression occurring with exercise was observed with vitamin E therapy Thus the data from serial maximal exercise treadmill tests on these 48 subjects with angina pectoris fail to demonstrate any significant improvement in exercise performance after 6 months of 1,600 I U d alpha tocopherol daily

Table II summarizes the results of the systolic time interval measurements made after 6 months of placebo and 6 months of vitamin E therapy The PEP/LVET is considered by most investigators to be the most sensitive systolic time interval index of left ventricular performance The increased PEP/LVET above the normal range (0.345 ± 0.036) in these 48 patients indicates diminished left ventricular performance was not significantly improved by vitamin E therapy There were 34 of the 48 (71 per cent) patients who had abnormally high PEP/LVET The PEP/LVET (0.452 ± 0.080 on placebo vs 0.439 ± 0.0?6 on vitamin E) in these 34 patients did not show significant decrease (p < 0.40) during vitamin E therapy The other systolic time interval indices as shown in Table II are remarkably similar during the two treatment phases These data fail to show any effect on left ventricular performance of the vitamin E therapy

Table III summarizes the data obtained from the daily angina diaries of the 48 patients There was a slightly greater incidence of angina during the 6 months of vitamin E (7.3 ± 12.6 pains per week) than during the 6 month placebo phase (6.7 ± 10.5 pains per week) but the difference is too small to be statistically significant No patient became free of angina during vitamin E therapy The nitroglycerin consumption was remarkably similar during the two 6 month treatment phases Five of the 48 patients showed as much as 50 per cent reduction in the frequency of their pains during vitamin E but six patients showed similar reduction in their chest pain

REFERENCES

1 Marks J Critical appraisal of the therapeutic value of alpha tocopherol Vitam Horm 20 573 1962
2 Vogelsang A and Shute E Effect of vitamin E in coronary heart disease Nature 157 772 1946
3 Shute W E Shute E V and Vogelsang E Vitamin E in heart disease Med Rec 160 91 1947
4 Vogelsang A Twenty four years using alpha tocopherol in degenerative cardiovascular disease Angiology 21 275 1970
5 Toone W M Effects of vitamin E Good and bad N Engl J Med 289 9 9 1973
6 Anderson T W Vitamin E in angina pectoris Can Med Assoc J 110 401 1974
7 Rinzler S H Bakst H Benjamin Z H Bobb A L and Travell J Failure of alpha tocopherol to influence chest pain in patients with heart disease Circulation 1 288 1950
8 Ravin I S and Katz K H Vitamin E in three treatment of angina pectoris N Engl J Med 240 331 1949
9 Makinson D H Oleesky S and Stone R V Vitamin E in angina pectoris Lancet 1 301 1948
10 Hove E L Hickman K and Harris P L The effect of tocopherol and of fat on the resistance of rats to anoxic anoxia Arch Biochem 8 395 1945
11 Telford I R Wiswell, O B and Smith E L Tocopherol prophylaxis in multiple exposures to hypoxia Soc Exp Biol Med 87 16 1954
12 Houchins, O B and Mattill, H A In vitro effect of alpha tocopherol phosphate on oxygen consumption of muscle from vitamin E-deficient animals Pro Soc Biol Med 50 216 1942
13 Zierler K L Folk B P Eyzaquirre C Jarcho L W Grob D and Lilienthal J L On certain effects of alpha tocopheryl phosphate on oxidative mechanisms of striated muscle Ann N Y Acad Sci 52 187 1949
14 Puente Dominguez J L and Dominguez R La accion de la vitamin E en el infarto de miocardia estudio experimental Rev Espan Cardiol 9 30 1955
15 Zierler K L Grob D and Lilienthal J L On the antithrombin and antiproteolytic activity of alpha tocopherol phosphate Am J Physiol 153 127 1948
16 Kay J H Hutton S B Weiss G N, and Ochsner A Studies on a antithrombin Surgery 28 24 1950
17 Shute E V, Vogelsant A B Skelton F R and Shute W E The influence of vitamin E on vascular disease Surg Gynecol Obstet 86 1 1948
18 Suffel P The use of alpha tocopherol in acute and subacute thrombophlebitis Can Med Assoc J 74 715 1956
19 Williams H T G Fenna D and Macbeth R A Alpha tocopherol in the treatment of intermittent claudication Surg Gynecol Obstet 132 662 1971
20 Shute W E On tailoring the dose of alpha tocopherol for cardiac patients, Summary 19 15 1967
21 Nair P P Identification of alpha tocopherol from tissues by combined gas-liquid chromatography mass spectometry and infrared spectoscopy Arch Biochem Biophys 127 413 1968
22 Weissler A M and Garrard C L Systolic time intervals in cardiac disease Mod Concepts Cardiovasc Dis 40 1 1971
23 McDonough J R and Bruce R A Maximal exercise testing in assessing cardiovascular function J South Carolina Med Assoc 65 26 1969
24 Bruce R A Kusumi, F and Hosmer D Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease AM HEART J 85 546 1973
25 Dagenais G R Pitt B and Ross R S Exercise tolerance in patients with angina pectoris Am J Cardiol 28 10 1971
26 Lapin E S Murray J A Bruce R A and Winterschied L Changes in maximal exercise performance in the evaluation of saphenous vein bypass surgery Circulation 47 1164 1973
27 Robinson B F Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris Circulation 35 1073 1967
28 Aronow W S The medical treatment of angina pectoris II Design of an antianginal drug study AM HEART J 84 132 1972

2 43 ± 0 99 mg per 100 ml during vitamin E phase

No deleterious side effects were observed resulting from the use of vitamin E during this study There were slightly more complaints of mild gastrointestinal disturbance during placebo phase (6 per cent) than during vitamin E phase (4 per cent) No exacerbation of hypertension, congestive heart failure or skeletal muscular complaints could be attributed to vitamin E therapy The various blood studies as listed under methods showed no significant differences between the two treatment phases

Discussion

Earlier studies of vitamin E failed to include many of the features which are now considered essential in a well designed study of an antianginal drug Of the previous evaluations of this agent only three included the important feature of double blinding in the protocol design The results of these three studies of the beneficial effects of vitamin E for angina patients were one some benefit one possible benefit and one no benefit The conflicting and inconclusive nature of prior reports appears to be due to the fact that only relatively small numbers of patients were studied, a cross over experimental design was not utilized the diagnosis of angina pectoris was not corroborated by requiring clear evidence of obstructive coronary disease in every patient the studies were not confined to those patients with both reproducible chest pain and ECG evidence of ischemia on exercise testing, and response to therapy was not measured in a quantitative way (for example by serial maximal exercise testing or by serial systolic time interval measurement) A double blind cross over study such as the present one in which each patient serves as his own control is particularly appropriate in studying an antianginal agent because of the wide variation in frequency and severity of chest pains in subjects with angina The exacerbations and spontaneous remissions of chest pains in patients with angina make evaluation of an antianginal agent difficult but inclusion of sufficient numbers of patients and use of a prolonged treatment trial as was done in the present study has minimized this potential problem

The purpose of the present report has been to use quantitative methods in subjects with proved obstructive coronary disease to determine whether or not 1 600 I U of *d* alpha tocopherol daily for 6 months produces any measureable improvement in 48 patients with stable angina pectoris Serial multistage exercise testing plus serial systolic time interval measurements which were performed on all patients participating in the study, allowed objective quantitative evaluation of the effects of vitamin E therapy in patients with angina pectoris The subjective and symptomatic antianginal effects of this agent have been measured by having patients keep a careful diary record of all angina attacks and the number of nitroglycerin tablets used While there is no evidence of any adverse effect due to vitamin E therapy, it is clear from the data presented that this treatment program failed to produce statistically significant improvement in any of the parameters studied in patients with established angina pectoris

Summary

Because of previous reports of the beneficial effect of vitamin E in angina pectoris patients, 48 patients with both stable angina and positive (chest pain plus ischemic ST depression) maximal exercise treadmill tests participated in a double-blind cross over study of 6 months of vitamin E and 6 months of placebo therapy separated by a 2 month no treatment period All 48 patients had positive selective coronary arteriograms (75 per cent obstruction of at least a major coronary artery) and/or Q wave ECG evidence of previous myocardial infarction (Minnesota criteria) Evaluation of drug effectiveness was based on performance of serial maximal exercise treadmill tests serial systolic time interval measurements and daily angina diaries No statistically significant differences between the two treatment periods were found in any of the parameters studied It is concluded that a large dose of vitamin E (1 600 I U of *d* alpha tocopherol succinate daily) for 6 months in patients with stable angina pectoris fails to increase the exercise capacity improve left ventricular function or reduce the frequency of chest pain

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a history of chest pain compatible with ischemic heart disease as well as sufficient clinical evidence to warrant coronary angiography. The patients with recent myocardial infarctions and those with left ventricular conduction defects were excluded. All patients had at least one coronary vessel narrowed by greater than 50 per cent. The systolic time intervals were measured usually within 24 hours before or after the procedure; however, some were as long as 36 hours, although the difference in time between the cardiac catheterization and the measurement of systolic time intervals apparently made no difference in the results, as will be pointed out subsequently.

Recording methods. The method for recording the carotid pulse in this laboratory has been previously described; it consists of a glycerin pellet strapped to the neck by a wide elastic band. A short piece of Tygon tubing connects the pellet to a Statham PM5 0.2 350 transducer. The heart sounds are recorded simultaneously from the aortic area with a filtered Altec Lansing microphone No. 525 A. The output of these transducers is amplified and recorded by an Electronics for Medicine DR 8 recorder. The output of each channel is connected directly into an on-line computer system and simultaneously recorded on analogue tape for future processing on the system if necessary. The on-line computer system is constructed as previously described, but there are a few improved features that should be pointed out. (1) There is a person built into the computer loop so that only quality records are selected for analysis. (2) The programs have been written to recognize the QRS complex in the electrocardiogram, the upstroke of the carotid pulse, the incisural notch, and the second heart sounds, and to automatically calculate the systolic time intervals. (3) The locations of the various points are then marked and displayed on the memory scope so that the individual in the computer loop has the prerogative of either accepting or rejecting the data or redigitizing the records. This assures quality control of each record and offers a standardized method for determining the systolic time intervals. The individual who operates the on-line system has been working with noninvasive technique for over ten years and is competent in recognizing the quality of the curves as well as correct locations of the carotid upstroke, the second heart sounds, the incisural notch, and the onset of the QRS complex. The accuracy of the program is such that only a very small percentage (approximately 5 per cent) has to be corrected. The time intervals are averaged from approximately ten complexes.

Table I. Correlation between computer measured and hand measured systolic time intervals

	r	SE (msec)
Q-Q	0.993	17.7
PEP	0.849	2
CU-CIN	0.954	9.1
Q-S	0.929	10.3

Table II. Correlation coefficients relating ejection fraction to the systolic time intervals

	r*	p†
Pre-ejection period (PEP)	0.45	< 0.02
Δ PEP‡	0.32	< 0.01
Left ventricular ejection period (LVET)	0.44	< 0.01
Δ LVET§	0.33	< 0.01
PEP/LVET	0.55	< 0.01

*r = Coefficient of correlation.
†p = Significance of coefficient of correlation.
‡Difference between the predicted PEP from heart rate of the patient and the actual duration observed.
§Difference between the predicted LVET from heart rate of the patient and the actual duration observed.

Since the automatic process system briefly described above is not performed from hand measurements, a series of 25 normal subjects and 27 patients with coronary artery disease without dyskinetic areas of the myocardium are measured both ways. Table I presents the results. Note that there is a high correlation between the two methods and the differences are insignificant.

Quantitative angiocardiographic procedures were performed as previously described by Dodge and associates, using the biplane procedure. The ejection fraction is calculated by dividing the stroke volume by the end-diastolic left ventricular volume.

Results

Table II presents the results of the study, listing the coefficients of correlation of the various systolic time intervals along with the measured ejection fraction. The analysis also included patients having mitral regurgitation coexisting with ischemic heart disease. The statis

The use of the systolic time intervals for predicting left ventricular ejection fraction in ischemic heart disease

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In recent years the systolic time intervals have become popular particularly for use in evaluating left ventricular function Weissler and associates,[1] as well as others in the past, have shown that the duration of ejection (CU CIN) as determined from the carotid pulse has a significant relationship to stroke volume[2,3] In addition, Garrard and associates[4] have proposed a ratio of the pre ejection period (PEP) which is corrected for pulse wave transmission time divided by left ventricular ejection time (LVET) to offer a way of predicting left ventricular function This ratio was independent of heart rate and therefore appeared to be more easily used in this respect In fact a regression equation has been proposed for predicting the ejection fraction

One of the problems with any measurement from noninvasive techniques has been the lack of adequate quantitative data for comparison In fact, there is considerable debate as to the best method of evaluating ventricular function quantitatively in man The ejection fraction is only one method and it has its limitations Many investigators now believe that the ejection fraction is not always a good predictor of left ventricular function, particularly in the presence of mitral regurgitation Some patients may do well with low ejection fractions following surgery whereas others who have normal ejection fractions have some myocardial dysfunction after surgery Nevertheless, the ejection fraction has been and is one index of left ventricular function Recent studies in coronary artery disease have emphasized its usefulness, particularly in patients with ischemic heart disease who are being evaluated for a vein bypass procedure[5-8] Studies have indicated that those patients with low ejection fraction are often a poor risk surgically A low ejection fraction has been used to differentiate those patients who may not benefit from the proposed surgical procedure[9] The original data on prediction of the ejection fraction from the PEP/LVET ratios appeared promising[4] however the data were collected on a wide variety of patients with various types of heart disease and the patient sample was relatively small The purpose of this paper is to report our study of the various systolic time intervals in relationship to the ejection fraction in patients with ischemic heart disease

Methods

Patient selection Patients were selected on the basis of availability of systolic time intervals and quantitative angiocardiography to determine the actual ejection fraction Only those patients with ischemic heart disease were included ($N = 306$) however 82 of these also had other cardiac lesions such as mitral regurgitation The series was studied altogether and in various categories as well The records have been accumulated in this laboratory over the last 5 years All patients gave

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and several distinctions can be noted The poorest correlations were obtained in those patients with cardiac enlargement and dyskinetic areas of the myocardium The second point is that there was essentially no difference between those systolic time intervals that were taken within a 24 hour period of cardiac catheterization and those that were taken between 24 and 36 hours

Discussion

The data presented in this paper indicate that although the systolic time intervals are related to left ventricular function as determined by the ejection fraction the correlation coefficients are so low and there is such a wide scatter of the data that it is not clinically safe to use any of these measurements in quantitating the ejection fraction The poorest relationship occurred in those patients with dyskinetic areas and cardiac enlargement (see Table III) The reason for this is obscure at this time The results of these data are disappointing since the original series certainly appeared to offer a simple means of obtaining one parameter of left ventricular function by a noninvasive technique[4] When one considers some of the physiological mechanisms which have previously been delineated by Wiggers concerning the phases of the cardiac cycle it becomes apparent that there are so many factors affecting the time intervals that it would be surprising if they would be of accurate value in quantitating only one parameter of ventricular function such as ejection fraction

The pre ejection period has been demonstrated to be affected by (1) heart rate (2) the rate of pressure rise in the left ventricle and (3) the diastolic aortic pressure as well as possibly the end diastolic ventricular pressure These last two factors in turn are affected by peripheral vascular resistance and left ventricular muscle stretch There are also probably other unknown factors participating in this system It should be pointed out that the pre ejection period appears to be least affected by heart rate however heart rate does play a small role in determining the duration of the PEP Therefore correcting the heart rate alone cannot adjust for all of the other physiological variables

Left ventricular ejection time (LVET) is more closely related to heart rate than the pre ejection period LVET is also affected by other physiologic variables such as peripheral vascular resistance

Table III Coefficient of correlation relating PEP/LVET with ejection fraction

No of days from catheterization	*No of patients*	*Coefficient of correlation*	*p value*
Coronary artery disease with no dyskinetic areas and no heart enlargement			
0-1	42	0.3[illegible]	< 0.05
2+	31	0.41	< 0.02
All patients	73	0.47	< 0.01
Coronary artery disease with dyskinetic areas			
0-1	66	0.42	< 0.01
2+	62	0.62	< 0.01
All patients	128	0.54	< 0.01
Coronary artery disease with dyskinetic areas and cardiac enlargement			
0-1	10	0.27	N.S†
2+	13	0.40	N.S
All patients	23	0.21	N.S
All patients above	2[illegible]4	0.44	< 0.01

Includes only those patients with ischemic heart disease alone
†N.S = not significant.

(afterload) stroke volume and rate of ventricular pressure rise as well as the degree to which the left ventricular contraction is sustained Although it has been demonstrated that a poor functioning left ventricle is not able to sustain ejection for as long a period of time as can a normal ventricle nevertheless it is possible that this is not always true Other factors also could affect LVET such as myocardial muscle fiber length afterload and the contractile state of the ventricle The effects of these factors have been well documented in studies using papillary muscle preparations[13] Thus there are still a number of physiological variables which affect the duration of phases of the cardiac cycle all of which are not directly related to ventricular contractility or function per se

An additional comment should be made concerning the use of the systolic time intervals in evaluating left ventricular function i e the present paper is simply a study of a series of patients with documented ischemic heart disease and does not include many other forms of cardiac abnormalities It remains a possibility that there may be a better correlation in other conditions than reported in this particular study The correlations in this paper are presented to illustrate the

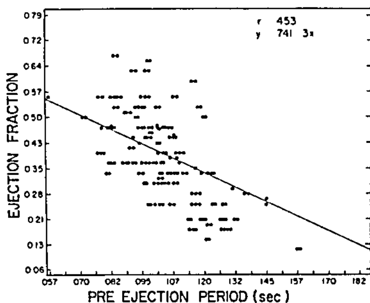


Fig 1 Scattergram of the pre ejection period and the known ejection fraction as determined by the angiocardiographic technique The r value is 0 453 with a p value of 0 01 The scatter is too large to use the pre ejection period time as a means of accurately predicting ejection fraction The regression line is presented as well as the equation

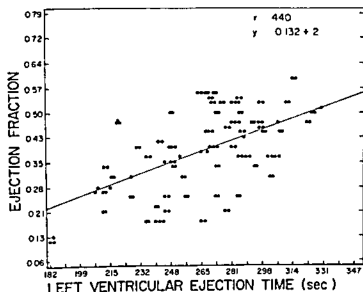


Fig 2 Scattergram of the left ventricular ejection time in a group of patients with ischemic heart disease against the measured ejection fraction by the angiocardiographic technique Notice the wide range of scatter The coefficient of correlation was 0 440 which is significant but the scatter is so great that the left ventricular ejection time is certainly not useful in accurately predicting the left ventricular ejection fraction The regression line is presented as well as the equation

tical significance of the correlation coefficients is also presented It is to be noted that all of the coefficients of correlation are low The highest coefficients of correlation was the PEP/LVET coefficient of correlation was the PEP/LVET ratio (0 55) The coefficient of correlation for the

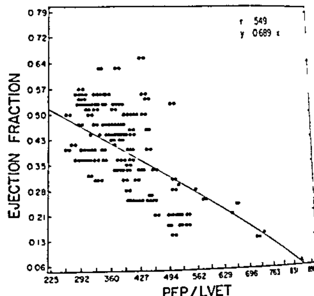


Fig 3 Scattergram of the PEP/LVET ratio plotted against the known ejection fraction The coefficient of correlation is better than the pre ejection period or ejection period alone having an r value of 0 549 which is significant The scatter is too great for using the PEP/LVET ratio for accurately predicting the ejection fraction The regression line is included as well as the equation

pre ejection period was 0 45 and when corrected for heart rate (Δ PEP) the correlation coefficient decreases to 0 32 However, correcting the left ventricular ejection time period for heart rate with the delta value, as proposed by Weissler decreased the coefficient of correlation from 0 44 to 0 33

Fig 1 presents the scattergram of the correlation between the ejection fraction and the pre ejection period (PEP) Fig 2 represents the left ventricular ejection time (LVET) compared to the ejection fraction Fig 3 presents the PEP/LVET ratio vs the *observed* ejection fraction The data in Fig 3 appear nonlinear, however a curvilinear fit only improved the coefficient of correlation to 0 60 Thus it did not appear significantly useful to pursue this approach further

Because it is possible that the presence of dyskinetic areas in the myocardium in this group of patients might affect the correlation between the systolic time interval and the ejection fraction the patients with only ischemic heart disease and no other abnormality were subsequently divided into several categories Also the time interval between cardiac catheterization and measurement of systolic time interval was determined to see if this influenced the coefficient of correlation between the PEP/LVET ratio and the ejection fraction Table III presents the data

nd several distinctions can be noted. The poorest orrelations were obtained in those patients with ardiac enlargement and dyskinetic areas of the myocardium. The second point is that there was ssentially no difference between those systolic ime intervals that were taken within a 24 hour period of cardiac catheterization and those that were taken between 24 and 36 hours.

Discussion

The data presented in this paper indicate that although the systolic time intervals are related to left ventricular function as determined by the ejection fraction, the correlation coefficients are so low and there is such a wide scatter of the data that it is not clinically safe to use any of these measurements in quantitating the ejection fraction. The poorest relationship occurred in those patients with dyskinetic areas and cardiac enlargement (see Table III). The reason for this is obscure at this time. The results of these data are disappointing since the original series certainly appeared to offer a simple means of obtaining one parameter of left ventricular function by a noninvasive technique.[4] When one considers some of the physiological mechanisms which have previously been delineated by Wiggers concerning the phases of the cardiac cycle, it becomes apparent that there are so many factors affecting the time intervals that it would be surprising if they would be of accurate value in quantitating only one parameter of ventricular function such as ejection fraction.

The pre-ejection period has been demonstrated to be affected by (1) heart rate, (2) the rate of pressure rise in the left ventricle, and (3) the diastolic aortic pressure, as well as possibly the end diastolic ventricular pressure. These last two factors in turn are affected by peripheral vascular resistance and left ventricular muscle stretch. There are also probably other unknown factors participating in this system. It should be pointed out that the pre-ejection period appears to be least affected by heart rate; however, heart rate does play a small role in determining the duration of the PEP. Therefore correcting the heart rate alone cannot adjust for all of the other physiological variables.

Left ventricular ejection time (LVET) is more closely related to heart rate than the pre-ejection period. LVET is also affected by other physiologic variables such as peripheral vascular resistance (afterload), stroke volume, and rate of ventricular pressure rise, as well as the degree to which the left ventricular contraction is sustained. Although it has been demonstrated that a poor functioning left ventricle is not able to sustain ejection for as long a period of time as can a normal ventricle, nevertheless it is possible that this is not always true. Other factors also could affect LVET, such as myocardial muscle fiber length, afterload, and the contractile state of the ventricle. The effects of these factors have been well documented in studies using papillary muscle preparations.[3] Thus there are still a number of physiological variables which affect the duration of phases of the cardiac cycle, all of which are not directly related to ventricular contractility or function per se.

Table III Coefficient of correlation relating PEP/LVET with ejection fraction*

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An additional comment should be made concerning the use of the systolic time intervals in evaluating left ventricular function, i.e., the present paper is simply a study of a series of patients with documented ischemic heart disease and does not include many other forms of cardiac abnormalities. It remains a possibility that there may be a better correlation in other conditions than reported in this particular study. The correlations in this paper are presented to illustrate the

fact that although there is a relationship between the systolic time intervals and the observed ejection fraction, the scatter of the data is so diverse that one can only conclude that it would be hazardous to use any regression equation for predicting the ejection fraction from the observed systolic time intervals in patients with ischemic heart disease

Summary

A large series of 306 patients with ischemic heart disease was studied with automated systolic time intervals and left ventricular ejection fraction as determined by the angiocardiographic method It was found the pre ejection period, left ventricular ejection time, delta values and PEP/LVET ratio all were related to the ejection fraction However in all instances the correlation was too low and the scatter of the data was too large to warrant the use of the systolic time intervals for predicting left ventricular function as indicated by the ejection fraction

Appreciation is expressed to Dr William P Hood Director Cardiac Catheterization Laboratory University Hospital and Dr John H Holt Jr Director Cardiac Catheterization Laboratory Veterans Administration Hospital for supplying the hemodynamic data used in this manuscript Appreciation is also expressed to Miss Lucile Romey for her contribution in obtaining the systolic time intervals

REFERENCES

1 Weissler A M Harris W S and Schoenfeld C D Systolic time intervals in heart failure in man Circulation 37 149 1968
2 Wiggers C J Circulation in health and disease, ed 1, Philadelphia 1923 Lea & Febiger Publishers
3 Willis K Eddleman E E Jr Acker J K Parks E and Heyer H F Variations in the duration of phases of the cardiac cycle in normal hearts as studied by the electrokymograph AM HEART J 40 485 1950
4 Garrard C L Jr Weissler A M and Dodge H T The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease Circulation 42 455 1970
5 Hammermeister K E and Kennedy J W Predictors of surgical mortality in patients undergoing direct myocardial revascularization Circulation 49 50(Suppl II) 112 1974
6 Young W G Jr Sabiston D C Jr Ebert, P A, Oldham H N Behar V S Kong Y Peter R H and Morris J J Jr Preoperative assessment of left ventricular function in patients selected for direct myocardial revascularization Ann Thoracic Surg 11 395 1971
7 Oldham H N Jr Morris J J Jr Rosati R A and Sabiston D C Jr Risk factors in coronary artery bypass surgery Arch Surg 105 918 1972
8 Collins J J Jr Cohn L H, Sonnenblick, E H Herman M V Cohn P F and Gorlin R Determinants of survival after coronary artery bypass surgery Circulation 47 48(Suppl III) 137 1973
9 Swatzell R H Jr Bancroft W H Jr Macy J Jr and Eddleman E E Jr The on line computer system for determining the systolic time intervals Comput Biomed Res 6 465 1973
10 Dodge H T Sandler H Ballew D H and Lord J D Jr Use of biplane angiocardiography for the measurement of left ventricular volume in man AM HEART J 60 762 1960
11 Wiggers C J Physiology in health and disease Philadelphia 1934 Lea & Febiger Publishers
12 Wiggers C J Studies on the consecutive phases of the cardiac cycle II The laws governing the relative durations of ventricular systole and diastole Am J Physiol 56 439 1921
13 Henderson A H Brutsaert D L Parmley W W and Sonnenblick E H Myocardial mechanics in papillary muscles of the rat and cat Am J Physiol 217 1273 1969

Further observations on the syndrome of idiopathic infantile hypercalcemia associated with supravalvular aortic stenosis

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Detroit Michigan

The syndrome of supravalvular aortic stenosis (SVAS) has been the subject of numerous reports and the role of idiopathic infantile hypercalcemia (IIHc) in its pathogenesis has been explored Experience gained with the entity has allowed broadening of the spectrum of its cardiovascular manifestations considerably to include a number of abnormalities not reported in the initial descriptions and not detected in the experimental model The purpose of this communication is twofold to catalogue the cardiovascular abnormalities currently recognized to occur with the syndrome and to add several previously unpublished observations which add further to the scope of the problem

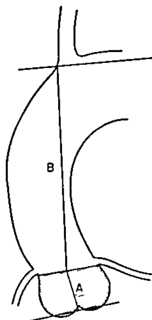
Subjects and methods

Seven children with features indicating the SVAS IIHc syndrome have been seen at the Henry Ford Hospital since 1961 No new registrants however have been diagnosed since 1968 The profiles of the seven patients comprising the study are outlined in Table I

All the children were significantly mentally retarded and all had the characteristic facial features associated with SVAS IIHc Each had a personality trait best described as overly affectionate and trusting All were Caucasian five were girls Their ages at first examination ranged from 7 months to 3 years 2 months

Each patient underwent at least one cardiac catheterization with right and left heart study and pertinent angiography Six patients had two or more hemodynamic studies allowing evolutionary evaluation of the physiologic alterations (Table II)

Measurement of the ascending aorta in the frontal and left anterior oblique views from the projected cineangiocardiograms was performed and compared with a series of control patients matched for age and weight The control individuals had forms of acyanotic congenital cardiac malformations not reported to be associated with primary aortic abnormalities Two measurements of the ascending aorta were made and compared as a ratio of segment length (Fig 1) The measurement *A* is the length of the line which bisected lines drawn through the aortic valve leaflets at



CONTROL 0 210 0 340
MEAN 0 265
SVAS 0 474 0 580
MEAN 0 510

Fig 1 (See text)

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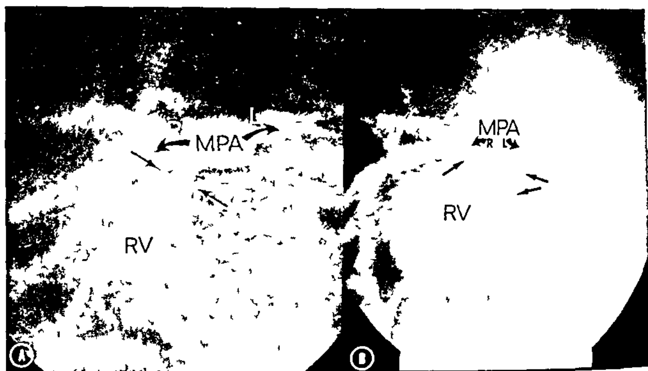


Fig 2 Single frames of right ventricular (RV) cineangiocardiograms *(A)* Case 1 Left anterior oblique projection The marked narrowing in the outflow tract of the *RV* is clearly seen (opposing arrows) The main pulmonary artery *(MPA)* and right pulmonary artery (arrow *R*) appear normal in size The left pulmonary artery (arrow *L*) is reduced in size and prominently kinked indicating pulmonary arterial stenosis confined to this vessel *(B)* Case 3 Frontal projection Distinct evidence for significant subpulmonary obstruction is seen within the RV (arrows) The *MPA* is of normal size but proximal right and left pulmonary arterial (arrows *R* and *L*) stenosis of mild degree is present

Table I Patient information

Case No	*Age*		*Typical facies*	*History suggesting hypercalcemia*	*IQ*	*EEG*	*Chromosomes*	*Serum calcium*
	First visit	*Last visit*						
1	7/12	12 1/12	+	+ +	53	N	N	–
2	1 9/12	9 6/12	+	+	55	N	N	–
3	2/12	6	+	+ +	66	–	–	–
4	1 6/12	7 6/12	+	+	62	N	N	–
5	3 2/12	8	+	+	59	N	–	5?/6
6	1 6/12	13 4/12	+	+	–	–	N	91 110 96 99 Age 5-13
7	2 9/12	2 9/12	+	+	–	–	–	–

+ + = Evidence of reduced fetal activity in utero in addition to positive extrauterine findings N = normal – = not performed

their lowest diastolic position and the level of the coronary arterial takeoffs This measurement was considered as the aortic root Measurement *B* is the length of the ascending aorta as measured from the bisection of the line at the coronary arterial level to the origin of the anterior wall of the innominate artery The *A/B* ratios were then compared in the SVAS and control groups

Other observations at the time of cardiac catheterization were made Particular attention was paid to the appearance of the right ventricular outflow tract and the pulmonary arterial tree during right heart study Additional malformations were sought hemodynamically and angiocardiographically from both sides of the heart and the great vessels (Table III)

Results

Right ventricular outflow obstruction Four infants showed evidence for obstruction to right

Table II Findings at cardiac catheterization

Case No	Age at catheterization			Hemodynamic findings			A/B
	1	*2*	*3*	*1*	*2*	*3*	
1	7/12	2 8/12	12	RA 9 RV 90/0/8	RA 6 RV 50/0/10 MPA 35/10 LA 12	RA 6 RV 30/0/8 MPA 26/11 LPA 29/9 LV 152/0/20 PA AO 126/90 DA AO 114/77	0 48
2	1 9/12	5 8/12		RA7 RV 45/0/10 PA 20/12 LV 150/0/16 A.AO 140/85	RA 6 RV 20/0/6 PA 18/9 LV 130/0/18 A AO 118/84		0 515
3	2/12	4		RA 4 RV 70/0/12	RA 3 RV 20/0/3 PA 22/10 LV 82/0/6 A.AO 80/40		0 58
4	1 6/12	6		RA 3 RV 55/0/6 PA 25/9 LA 6	RA 3 RV 20/0/5 PA 20/10 LV 124/0/10 A.AO 110/85		0 48
5	3 2/12			RA 4 RV 30/0/10 PA 28/11 LV 180/10/12 A.AO 120/60			0 57
6†	1 6/12	6 10/12	13 4/12	RA 6 RV 42/0/7 MPA 38/12 LV 124/0/16 A.AO 102/58	LV 164/0/10 A.AO 110/76	RA 2 RV 23/0/7 MPA 23/4 RPA 16/6	0 474
7	2 9/12	11		RA 6 RV 78/0/10 MPA 80/5 LA 7 LV 160/0/5	RA 4 RV 38/1/8 MPA 19/11 RPA 17/8 LV 140/2/11 PA AO 134/64 DA AO 110/66		0 475

Abbreviations RA, right atrium LA left atrium RV right ventricle LV left ventricle PA pulmonary artery (main right left) A.AO ascending aorta PA AO proximal ascending aorta DA AO distal ascending aorta A/B ratio of aortic segments at angiography
†Aortic gradient progressed, surgical repair at age 7

ventricular outflow (cases 1 to 4 Fig 2) In the two most severe of these the pulmonary artery could not be entered but the right ventricular pressures were near systemic levels at an age that normal pulmonary arterial resistances and pressures would have been expected Repeat cardiac catheterization in all four children 2 to 4½ years later revealed absence of (cases 2 to 4) or marked diminution in the gradient (case 1) and repeat right heart catheterization 11½ years later confirmed the absence of an outflow gradient in this case also Thus transient systolic gradients across the right ventricular outflow tract were confirmed to occur although the initial cause and subsequent cessation remain unexplained

Ascending aortic length In all the children the

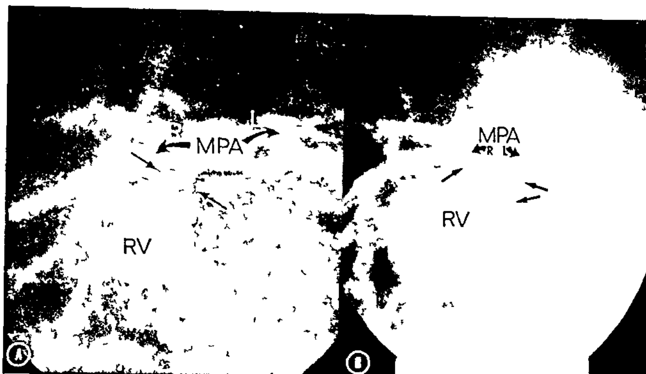


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2	1 9/12	9 6/12	+	+	55	N	N	–
3	2/12	6	+	+ +	66	–	–	–
4	1 6/12	7 6/12	+	+	62	N	N	–
5	3 2/12	8	+	+	59	N	–	5 2/6 9 1 11 0
6	1 6/12	13 4/12	+	+	–	–	N	9 6-9 9 Age 5-13
7	2 9/12	2 9/12	+	+	–	–	–	–

+ + = Evidence of reduced fetal activity in utero in addition to positive extrauterine findings N = normal – = not performed

their lowest diastolic position and the level of the coronary arterial takeoffs This measurement was considered as the aortic root Measurement *B* is the length of the ascending aorta as measured from the bisection of the line at the coronary arterial level to the origin of the anterior wall of the innominate artery The *A/B* ratios were then compared in the SVAS and control groups

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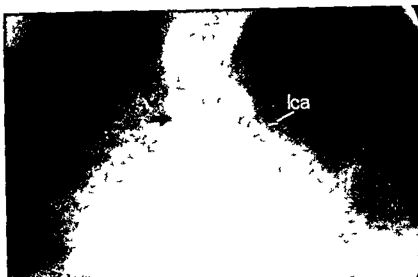


Fig 4 Single frame from cineaortogram Case 1 Diastole Left anterior oblique projection. A single large aortic valve leaflet is seen The left coronary artery (arrow *lca*) arises from a dilated sinus of Valsalva The right coronary artery is not seen Solid arrow indicates the minimal supravalvular narrowing

gross inspection of the aortograms revealed a typical configuration The brachiocephalic vessels appeared elongated and rose from an aortic arch which seemed displaced inferiorly in the thorax giving the impression of shortening of the ascending portion of the aorta (Fig 3) The ratio of the aortic root to the ascending aortic segment (*A/B* Fig 1) was distinctly greater for these seven patients (0 474 to 0 580) than for normal values for this laboratory from a series of comparable children with other forms of noncyanotic congenital cardiac malformations (0 230 to 0 340) The p value for this comparison was $< 0\ 05$ These data indicate that there is an over all shortening of the ascending aorta and the degree of this shortening appears to bear no relation to the severity of the supravalvular stenosis (Table II)

Other cardiovascular malformations Several additional abnormalities exclusive of pulmonary arterial stenosis which occurred in four children were found Two of these significant valvular aortic stenosis and mitral valvular regurgitation occurred simultaneously in case 1 The aortic valve was grossly deformed with total absence of normal cusp structure (Fig 4) Only one large sinus of Valsalva could be positively identified in any projection Coronary arterial origin appeared normal The mitral annulus appeared widened and eccentric Although no distinct leaflet prolapse could be identified left ventricular contraction was unusual with prominent constriction of the region of origin of the anterior papillary muscle as seen in some cases with the midsystolic click syndrome (Fig 5) Case 3 presented evidence angiographically of a typically positioned coarctation of the aorta

Other hemodynamic observations In two patients there was evidence for total resolution of a significant degree of pulmonary arterial stenosis (PAS) In case 1 the PAS was apparent angiographically and though seemingly not severe initially at restudy was totally absent Unfortunately the pulmonary artery was not entered in this case and thus no gradient recorded Case 7 however had significant hypertension in the main pulmonary artery at the first study and although a gradient to the periphery was not measured restudy 8 years later revealed normal pulmonary arterial pressures and no peripheral gradient

Progression to a more severe degree of aortic obstruction was recorded on serial left heart catheterization of case 6 In this instance the systolic gradient across the area of supravalvular aortic stenosis more than doubled over a 5 year period and surgical correction was performed in view of this following its identification

Discussion

Of the two terms most commonly used to identify the syndrome only supravalvular aortic stenosis was uniform in these cases Indeed in

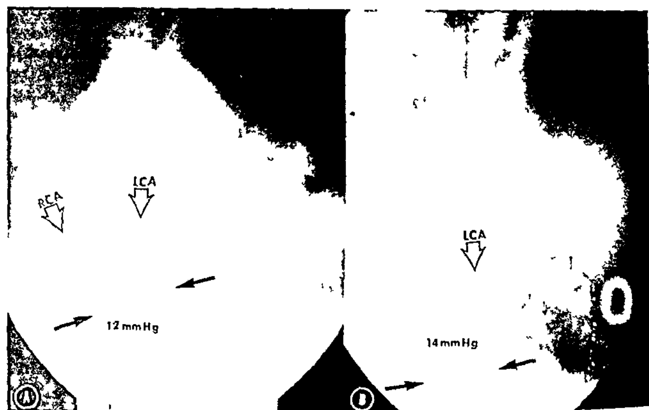


Fig 3 Single frames of cineaortograms left anterior oblique projection (*A*) Case 2 (*B*) Case 4 Note similar appearance of each aorta with apparent elongation of the brachiocephalic vessels after their origin from the aortic arch and the obvious ascending aortic shortening when compared with the aortic root segment measured between the aortic valve cusps (solid arrows) and the origins of the coronary arteries (arrows *LCS RCA*) Supravalvular gradient is indicated

Table III Summary of hemodynamic findings*

Case	*Age at catheterization*			*Catheterization*		
	1	*2*	*3*	*1*	*2*	*3*
1	7/12	2 8/12	12	RVO† PAS	RVO Red PAS Reg	RVO Ab MR AS Min SVAS
2	1 9/12	5 8/12		RVO PAS	RVO Ab	
3	2/12	4		RVO† PAS	RVO Ab Coarc Aorta	
4	1 6/12	6		RVO	RVO Ab Min SVAS	
5	3 2/12			Normal Right		
6	1 6/12	6 10/12	13 4/12	Mod SVAS PAS Min SVAS	Prog SVAS	
7	2 9/12	11		PAS Min SVAS	Reg I AS PPS Min SVAS	

Abbreviations RV right ventricle PA pulmonary artery RVO right ventricular outflow obstruction †pulmonary artery not entered Red reduced Ab absent PAS pulmonary arterial stenosis Reg regressive MR mitral regurgitation AS aortic valvar steno : SVAS supravalvular aortic stenosis Min minimal Mod moderate Prog progressive PPS valvular pulmonic stenosis

currence of right ventricular outflow obstruction which occurred to highly significant degree in two cases and to lesser degree in two but which was in all transient having disappeared by the age of 12 years in each instance The nature and cause of this is conjectural Angiographically it appeared to involve the crista supraventricularis A relationship to the presence of hypercalcemia in the infancy period although speculative at present is nonetheless an intriguing possibility Increase in inotropic action of the heart coincident with the administration of calcium is a recognized occurrence[20] The mechanism by which this occurs has been suggested to involve the endogenous release of catecholamines in the heart based on a finding in hamsters of a form of hereditary cardiomyopathy in which high levels of myocardial calcium are found The fact that the most significant degree of obstruction was present in the two individuals studied initially in infancy suggests some such relationship Indeed systolic murmurs have been commented upon in children with IIHc and in some instances these have either totally disappeared or regressed in intensity with age and normalized calcium levels a finding unexpected for SVAS[7, 2] Furthermore marked concentric myocardial hypertrophy was a finding at postmortem examination in one patient with IIHc described by Joseph and Parrott and as well by Rashkind Golinko and Arcasoy

Three additional malformations of the cardiovascular system were recorded in this series of patients and each has been noted by other investigators Thus mitral regurgitation or other mitral valvar abnormality has been reported in four other cases [3] aortic valvar abnormality in two and typical aortic coarctation in three instances As well generalized hypoplasia of the entire thoracic aorta has been noted to occur[1] [5] and systemic vascular coarctations other than those directly involving the aorta have been recorded In addition valvar pulmonic stenosis interventricular septal defect[1] [23] and atrial septal defect[1] have been mentioned

It is not within the scope of this communication to enter into a detailed review of the possible causes of the syndrome However the data collected from these patients do appear to have developmental significance and a brief discussion in view of our findings as well as those of others is in order

Any role played by fetal hypercalcemia per se in the production of the cardiovascular abnormalities observed is questionable As already mentioned hypercalcemia in infancy has by no means been a routine finding in these patients To the contrary most patients have been normocalcemic and as with the included cases hypercalcemia suggested by symptoms rather than by positive biochemical determination The commonly reported symptoms however are indeed those associated with proved hypercalcemia The issue is further clouded by the failure to find any of the cardiovascular abnormalities or the facial features seen with the syndrome in hypercalcemic progeny of hypocalcemic mothers or infants with familial hypercalcemia[2] even though the fetal parathyroid glands appear anatomically functional by the end of the first trimester of pregnancy indicating that hypercalcemia could result early in gestation[27]

The suggestion by Friedman and co workers [7] that vitamin D toxicity or sensitivity by the fetal/maternal unit may be causative does not appear to offer a totally satisfactory explanation for several reasons Hypercalcemia was not clearly present in the experimental material presented[30] The bone changes seen in the severe form of hypercalcemia were found to not be those associated with hypervitaminosis D [3] Also a history of anything other than normal vitamin D intake by mothers of the included patients as well as those reported by others has not been found [13, 1] [6] Previous or subsequent pregnancies of these women have not produced other examples of the syndrome even though the intake of vitamin D appears essentially the same

Finally the findings reported herein indicate much less specificity for a single causative agent than has been reported strongly suggesting a more complex etiology We consider more plausible then the possibility of hypercalcemia when present as another abnormality associated with the syndrome rather than an etiologic factor Thus whether or not hypercalcemia is related to the cause of the syndrome or is a secondary finding is not yet established Indeed whether it occurs frequently enough to be considered at all is open to question

Conclusion

Seven patients with features currently considered to be associated with SVAS and IIHc are



Fig 5 Single frame from left ventricular *(LV)* cineangiocardiogram Case 1 Right anterior oblique projection Marked asynchrony of contraction of the waist of the *LV* is seen (open arrow) The left atrium *(LA)* is greatly enlarged The level of the mitral valve annulus is identified by solid arrows

fantile hypercalcemia as evidenced by elevation of serum calcium levels was not sought in early life in any of the patients and only one child (case 5) was discovered at any time to have an alteration of calcium levels with several determinations indicating *hypocalcemia* However, all had symptoms in early life known to occur in children with hypercalcemia including irritability, vomiting, and hypotonia[1,5] and all had other somatic defects known to occur with the syndrome when hypercalcemia is present Thus, all were moderately handicapped mentally[1] five with tested low I Q values and two clinically determined as retarded All had facial characteristics of the syndrome[6,14] and all had postnatal growth failure[1, 4, 8, 9, 11, 14] Reliance on such clinical findings as these has characterized many of the reports of the syndrome with elevated calcium values lacking Indeed, the question as to whether hypercalcemia should be ever considered as a component of the syndrome has been raised[14] and many involved children have not been determined to have SVAS[1, 2, 7, 14]

SVAS, however is by most, closely linked with the syndrome and was the first cardiovascular defect recognized to occur with it[6, 8, 9, 1] This aspect of the aortic malformation has then, been amply described and needs no further comment Perhaps of equal or greater importance in view of the fact that the "stenosing ring may produce little or no gradient as evidenced by three of our cases is the finding of gross shortening of the ascending aorta above the level of the coronary ostia to the level of the first brachiocephalic vessel origination This finding was first commented upon by Perou[15] in 1961 in an autopsy case described as Marfan s syndrome which in retrospect likely represents the SVAS IIHc syndrome Kurlander and associates[16] have described the angiographic appearance with certain forms of SVAS commenting upon the apparent shortening of the ascending aorta "as judged by the distance between the aortic valve and the origin of the innominate artery without actual segmental measurements The gross radiographic appearance is best seen in Fig 3 and is the obvious discrepancy of the length of the brachiocephalic vessels compared with that of the aorta On reviewing the acceptable published aortograms from the literature this finding appears to be the most common single malformation of the aorta seen with this syndrome, perhaps more important from a diagnostic standpoint than a finding of actual stenosis

Pulmonary arterial stenosis is recognized to occur with this condition[10, 12, 17, 18] and its natural history has been well documented[19] Thus some regression with age of this abnormality is not totally unexpected Of considerable interest however is the previously unrecognized oc

Experimental and laboratory reports

Effectiveness of direct current defibrillation. Role of paddle electrode size

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Myocardial damage from direct current (DC) defibrillator discharges is less when repetitive discharges are delivered by paddle electrodes (PE's) that are 12.8 cm in diameter as opposed to PE's that are 8.0 or 4.3 cm in diameter. The present study was undertaken to determine if the larger 12.8 cm diameter PE's are as effective as the 8.0 cm diameter PE's in defibrillation.

The experiment was designed to determine defibrillation effectiveness by measuring the longest duration of ventricular fibrillation that could be successfully terminated by a single low energy DC countershock with either 12.8 or 8.0 cm PE's. The transthoracic impedance was measured with each countershock and correlated with defibrillation effectiveness.

Methods

Forty-five mongrel dogs ranging in weight from 13.5 to 31.5 kilograms (mean 21.1 ± 3.7) were anesthesized with pentobarbital 25 mg per kilogram given intravenously. The thoracic hair was removed with electric clippers and the chest was shaved. An endotracheal tube was inserted. A short transvenous catheter was inserted into the left femoral vein to draw blood for measurement of venous pH. A No. 4 French bipolar electrode catheter was placed into the right femoral vein and advanced into the right ventricle with intracardiac electrographic monitoring. Ventricular fibrillation was produced by passing a 1 second 60 Hertz current at ½ volt to the right ventricle via the bipolar electrode catheter.

Defibrillation countershocks were delivered by a direct current (DC) defibrillator (Hewlett Packard Model 7802C). The defibrillator meter setting was 50 watt-seconds. Transthoracic impedance was measured with each countershock by the method previously reported.[2,3] The average transthoracic impedance encountered with the first countershock was 55 ohms. At this impedance the average delivered energy was 32 watt-seconds. Redux paste (Hewlett Packard part No. 651-1008-1) was used in liberal amounts on the paddle surfaces as PE-chest wall interface.[3] The defibrillator PE's were held firmly on opposing lateral aspects of the dog's thorax at the level of the point of maximal cardiac impulse. One of the two sizes of PE's was used on each dog. The larger PE's had a diameter of 12.8 cm. The smaller PE's were of a size typically found on most commercial defibrillators having a diameter of 8.0 cm. Twenty-three animals (mean weight 20.6 ± 3.2 kilograms) were defibrillated with the large PE and 22 animals (mean weight 21.5 ± 4.2 kilograms) with the standard PE.

Following the induction of ventricular fibrillation the time interval before the first attempted defibrillatory countershock was 15 seconds. If the first countershock failed to defibrillate the animal, it was assigned a duration of zero seconds and eliminated from further testing. If defibrillation was achieved with the first countershock, the second trial was undertaken. On the second trial defibrillation was attempted 30 seconds after

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reported Hypercalcemia was not proved in any instance The most striking anatomic finding was shortening of the aortic segment between the coronary arterial origins and the origin of the first brachiocephalic vessel Transient subvalvular pulmonic stenosis was found in each of four infants Other associated cardiovascular abnormalities included aortic valvar stenosis, mitral valvar abnormality with regurgitation and coarctation of the aorta

The author is indebted to Dr John R Morgan T C Thompson Children s Hospital Chattanooga Tennessee for the follow up catheterization data on patient seven

REFERENCES

1 Schlesinger B E Butler N R and Black J A Severe type of infantile hypercalcaemia Br Med J 1 127 1956
2 Bongiovanni A M Eberlein W R and Jones I T Idiopathic hypercalcemia of infancy with failure to thrive N Engl J Med 257 951 1957
3 Rashkind W J Colinko R and Arcasoy M Cardiac findings in idiopathic hypercalcemia of infancy J Pedi atr 58 464 1961
4 Najjar S S and Yazigi A Vitamin D intoxication in infants Environ Child Health 19 271 1973
5 Fraser D Kidd B S L Kooh S W and Paunier L A new look at infantile hypercalcemia Pediatr Clin North Am 13 503 1966
6 Black J A and Bonham Carter R E Association between aortic stenosis and facies of severe infantile hypercalcaemia Lancet 2 745 1963
7 Joseph M C and Parrott D Severe infantile hypercal caemia with special reference to the facies Arch Dis Child 33 385 1958
8 Williams J C P Barratt Boyes B G and Lowe J B Supravalvular aortic stenosis Circulation 24 1311 1961
9 Beuren A J Apitz J and Harmjanz D Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance Circulation 26 123, 1962
10 Beuren A J Schulze C Eberle P Harmjanz D and Apitz J The syndrome of supravalvular aortic stenosis peripheral pulmonary stenosis mental retardation and similar facial appearance Am J Cardiol 13 471 1964
11 Farrehi C Dotter C T and Griswold H E Supra valvular aortic stenosis Am J Dis Child 108 335 1964
12 Garcia R E Friedman W F Kaback M M and Rowe R D Idiopathic hypercalcemia and supraval vular aortic stenosis N Engl J Med 271 117 1964
13 Fay J E Lynn R B and Partington M W Supra valvular aortic stenosis mental retardation and a char acteristic facies Can Med Assoc J 94 295 1966
14 Jones K L and Smith D W The Williams Elfin facies syndrome J Pediatr 86 718 1975
15 Perou M L Congenital supravalvular aortic stenosis Arch Pathol 71 453 1961
16 Kurlander G J Petry E L Taybi H Lurie P R and Campbell J A Supravalvar aortic stenosis. Roentgen analysis of twenty seven cases Am J Roentgenol Radium Ther Nucl Med 98 782 1966
17 Jue K I Noren G R and Anderson R C The syndrome of idiopathic hypercalcemia of infancy with associated congenital heart disease J Pediatr 67 1130 1965
18 Ottesen O F Antia A U and Rowe R D Peripheral vascular anomalies associated with the supravalvular aortic stenosis syndrome Radiology 86 430 1966
19 Eldredge W J Tingelstad J B Robertson L W Mauck H P and McCue C M Observations on the natural history of pulmonary artery coarctations Circu lation 45 404 1972
20 Hamilton W F and Dow P Handbood of physiology Circulation Volume I Washington DC 196? American Physiological Society pp 165 171
21 Jasmin G and Solymoss B Prevention of hereditary cardiomyopathy in the hamster by Verapamil and other agents (38771) Proc Soc Exp Biol Med 149 193 1975
22 Daeschner G L and Daeschner C W Severe idiopath ic hypercalcemia of infancy Pediatrics 19 36? 195?
23 Page H L Jr Vogel J H K Pryor R and Blount S G Jr Supravalvular aortic stenosis Unusual obser vations in three patients Am J Cardiol 23 2?0 1969
24 Driscoll D J Friedberg D Z and Gallen W J Idiopathic hypercalcemic syndrome with mitral stenosis Wis Med J 73 115 1974
25 Vazquez A M Zuberbuhler J R and Kenny F M Mitral insufficiency in association with the syndrome of idiopathic hypercalcemia of infancy J Pediatr 73 90? 1968
26 Antia A U Wiltse H E Rowe R D Pitt E L Levin S Ottesen O E and Cooke R E Pathogenesis of the supravalvular aortic stenosis syndrome J Pediatr 71 431 1967
27 Aceto T Jr Batt R E Bruck F Schultz R B and Perez Y R Intrauterine hyperparathyroidism A complication of untreated maternal hypoparathyroid ism J Clin Endocrinol Metab 26 487 1966
28 Hillman D A Scriver C R Pedvis S and Shrago vitch I Neonatal familial primary hyperparathyroid ism N Engl J Med 270 483 1964
29 Friedman W F Vitamin D as a cause of the supraval vular aortic stenosis syndrome Am Heart J 73 ?18 1967
30 Friedman W F and Roberts W C Vitamin D and the supravalvar aortic stenosis syndrome The transpla cental effects of vitamin D on the aorta of the rabbit Circulation 34 77 1966
31 Friedman W F and Mills L F The relationship between vitamin D and the craniofacial and dental anomalies of the supravalvular aortic stenosis syndrome Pediatrics 43 12 1969
32 Nguyen V C Sennott W M and Knox G S Neonatal hyperparathyroidism Radiology 112 1?? 1974

The criterion for a successful trial was defibrillation. If the animal was defibrillated but was without a palpable arterial pulse, external cardiac massage and artificial ventilation were instituted. If these cardiopulmonary resusitative (CPR) measures were successful, that trial was deemed a successful defibrillation. If the animal could not be resuscitated, the trial was designated a failure. On the basis of these criteria, the longest duration of ventricular fibrillation terminated by successful defibrillation was recorded for each animal for the PE size used.

Student's t test (independent groups, two tailed) and chi square analysis were used to assess statistical reliability.

Results

The mean longest duration of ventricular fibrillation successfully terminated with the 12.8 cm diameter PE was 1.22 ± 1.05 minutes compared to 0.56 ± 0.67 minutes with the 8.0 cm diameter PE. This difference was significant ($p < 0.02$).

Experimental bias could have occurred during CPR in that a greater or more prolonged attempt to resuscitate could have disproportionately increased the number of successes for either the 12.8 cm PE or the 8.0 cm PE group. In an effort to remove the effect of CPR, the data were recalculated using only the trial before CPR was necessary. When this was done, the mean longest duration of ventricular fibrillation determined by a single countershock was 0.97 ± 0.69 minutes for the 12.8 cm PE and 0.52 ± 0.59 for the 8.0 cm PE group ($p < 0.05$).

Table I shows the relation of the mean transthoracic impedance (measured on the first countershock in each animal) to animal weight and paddle electrode size. For this analysis, the animals were divided into those whose weight was greater than 20 Kg and those whose weight was equal to or less than 20 Kg. This table confirms earlier observations that there is an inverse relation between paddle electrode size and transthoracic impedance.[3] A direct but insignificant relationship between dog size and transthoracic impedance was noted.

Defibrillation effectiveness was analyzed by comparing the per cent of defibrillation with the 12.8 cm vs 8.0 cm PE at each time interval (Tables II and III). During the first minute of ventricular fibrillation, the incidence of defibrillation with the large PE was 88 per cent, significantly greater than the 71.1 per cent incidence of defibrillation with the standard PE ($p < 0.04$). There was no statistically significant difference during or after the second minute of fibrillation. This may be related to the small number of animals surviving the first minute.

Another indication of enhanced effectiveness of the larger PE is that survival was distinctly more probable for animals in the large PE group (Table III).

When defibrillation effectiveness during the first minute of ventricular fibrillation was plotted against the measured transthoracic impedances (Fig. 1), a high correlation coefficient was found ($r = -0.94$). The mean transthoracic impedance associated with failure of defibrillation during the first minute was 57 ± 18 ohms, significantly higher than that of the animals in which the countershock was effective, 45 ± 13 ohms ($p < 0.02$).

Discussion

Tacker and Geddes and their associates[6] have shown that the electrical dose necessary for ventricular defibrillation of animals increases with increasing body weight[5] and that the threshold for ventricular defibrillation increases during the first 2 hours following coronary ligation.[6] A study of defibrillation in man revealed that commercially available direct current defibrillators may not deliver enough energy for defibrillation of heavy subjects. Direct current defibrillators in clinical use in 1971 varied considerably in the amount of energy delivered at settings of 400 watt seconds, i.e., 155 to 340 watt seconds against a 50 ohm resistance. Since then, many manufacturers have increased the energy output of their later models and defibrillators are available that deliver 580 watt seconds. Prototype commercial units have been developed that have the capability of delivering 1,000 watt seconds. Because of these developments, the observation that myocardial damage can occur from repetitive direct current defibrillator countershock delivering less than 300 watt seconds is important.

Myocardial damage from DC defibrillators relates both to the time interval between discharges and to the size of the paddle electrode used. Myocardial necrosis is less when repetitive

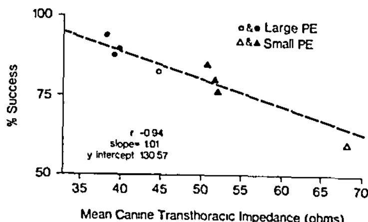


Fig 1 Defibrillation effectiveness during the first minute of ventricular fibrillation related to transthoracic impedance Open circles and triangles represent the mean impedance of the initial (i e following 15 seconds ventricular fibrillation) countershocks and the solid circles and triangles the mean impedance of the 30 45 and 60 second countershock

Table I Relationship of the transthoracic impedance to animal weight and paddle electrode size

Animal weight	*Paddle electrode diameter* (12.8 cm)	(8.0 cm)	Combined
Large (> 20 kg)	(A) 46.6 ± 9.1Ω (N = 8)	(B) 71.2 ± 12.3Ω (N = 10)	(A + B) 58.9 ± 16.1Ω
Small (≤ 20 kg)	(C) 43.3 ± 5.4Ω (N = 11)	(D) 61.9 ± 8.4Ω (N = 6)	(C + D) 52.6 ± 11.0Ω
Combined	(A + C) 44.9 ± 6.6Ω (N = 19)	(B + D) 66.5 ± 10.6Ω (N = 16)	

Corrected for unequal numbers
A vs B $p < 0.002$
A vs C ns
A vs D $p < 0.02$
B vs C $p < 0.001$
B vs D ns
C vs D $p < 0.002$
A + B vs C + D ns
A + C vs B + D $p < 0.001$

ventricular fibrillation was induced If defibrillation was achieved with the second countershock a third trial was undertaken If a single countershock failed to defibrillate the animal was assigned a duration of 15 seconds and eliminated from further testing On the third trial the defibrillation attempt was made after ventricular fibrillation had been allowed to proceed for 45 seconds In this manner the time interval between fibrillation and attempted defibrillation was increased by 15 second increments in each subsequent trial until failure was encountered

Between each two trials the electrocardiogram was monitored until any arrhythmia secondary to the defibrillation had abated The venous pH was measured and if the value dropped more than 0.05 the animal was given sodium bicarbonate in amounts necessary to increase the venous pH to ± 0.02 of the baseline venous pH This procedure required from 10 to 30 minutes after each trial

Table II Relation of the duration of ventricular fibrillation and paddle electrode size to successful defibrillation

Duration of ventricular fibrillation	*Defibrillation using 12.8 cm diameter PEs*	*Defibrillation using 8.0 cm diameter PEs*	*p value*
First minute (15 30 45 and 60 second trials combined)	66/75 (88%)	38/53 (71%)	$p < 0.04$
Second minute (75 90 105 and 120 second trials combined)	29/37 (78%)	10/16 (63%)	ns
Longer than 2 minutes	17/23 (74%)	1/2 (50%)	Insufficient numbers
All trials combined	112/135 (83%)	49/71 (69%)	$p < 0.04$

Table III Survival related to paddle electrode size

Duration of ventricular fibrillation (sec)	*12.8 cm PE survival rate*	*8.0 cm PE survival rate*	*p value*
15	19/23 (82.6%)	13/22 (59.1%)	ns
30	17/23 (73.9%)	10/22 (45.5%)	ns
45	16/23 (69.6%)	8/22 (36.4%)	$p < 0.06$
60	14/23 (60.9%)	7/22 (31.8%)	ns
76	10/23 (43.5%)	4/22 (18.2%)	Insufficient numbers
90	7/23 (30.4%)	3/22 (13.6%)	
105	6/23 (26.1%)	2/22 (9.1%)	
120	6/23 (26.1%)	1/22 (4.5%)	
135	5/23 (21/7%)	1/22 (4.5%)	
150	4/23 (17.4%)	0/22 (0%)	
165	3/23 (13.0%)		
180	2/23 (8.7%)		
195	2/23 (8.7%)		
210	1/23 (4.3%)		
225	0/23 (0%)		

tion of subjects in the 13 5 to 31 5 kilogram (29 to 69 pound) weight range than are paddle electrodes that are only 8 0 cm in diameter

The authors gratefully acknowled e the secretarial assistance of Mrs Beverly Luedke Ms Judy Hurley and Miss Ann Vallefuoco and the services of the Audiovisual Department of the Arizona Medical Center Drs Frank I Marcus and Bertron M Groves of the Section of Cardiology and Dr Emanuel Furst of Biomedical Engineering kindly reviewed the manuscript

REFERENCES

1 Dahl C F Ewy G A Warner E D et al Myocardial damage from direct current countershock Effect of paddle electrode size and time interval between discharges Circulation 50 956 1974
2. Ewy G A Fletcher R D and Ewy M D Comparative analysis of direct current defibrillators J Electrocardiol 5 349 1972
3 Connell P N Ewy G A Dahl C F et al. Transthoracic impedance of defibrillation discharge Effect of electrode size and electrode-chest wall interface J Electrocardiol 6 313 1973
4 Ewy G A Defibrillation output in Proceedings of Cardiac Defibrillation Conference Purdue University West Lafayette Indiana Oct 1975 pp 33-38
5 Geddes, L. A Tacker W A Rosborough J P., et al. The electrical dose for ventricular defibrillation of large and small animals using precordial electrodes, J Clin Invest 53 310 1974
6 Tacker W A., Geddes L. A Cabler P S et al. Electrical threshold for defibrillation of canine ventricles following myocardial infarction Am Heart J 88 4 6, 1974
7 Tacker W A Galioto F M Fiuliani E., et al Energy dosage for human trans-chest electrical ventricular defibrillation N Engl J Med 290 214 1974
8. Ewy G A Defibrillators defibrillation and cardioversion the cardiac arrhythmias, ed 2 St Louis, 1973, The C V Mosby Company chap 21
9 Geddes L. A Tacker W A., Rosborough J., et al. The increased efficacy of hi h energy defibrillation in Proc 10th Ann Scientific Sessions A.A M I., Boston 1975
10 Guyton A C and Satterfield J Factors concerned in electrical defibrillation of the heart particularly through the unopened chest Am J Physiol 167 81 1951

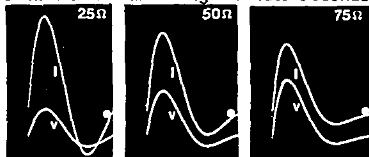


Fig 2 Simultaneous current (*I*) and voltage (*V*) waveforms from a Hewlett Packard 7802C defibrillator discharged with resistive loads of 25 50 and 75 ohms with defibrillator dial indicating stored energy of 100 watt seconds

discharges are delivered by paddle electrodes that are 12 8 cm in diameter as opposed to paddle electrodes that are 8 0 or 4 3 cm in diameter [1] If the use of larger paddle electrodes with DC countershock is safer it became necessary to know if they were as effective in defibrillation

Guyton and Satterfield[10] reported on factors concerned with transthoracic electrical defibrillation of the heart using alternating current They concluded that during the first minute defibrillation with optimal stimuli will probably restore normal circulation If epinephrine is used simultaneously this interval probably can be prolonged 30 seconds or more When the heart remains in fibrillation more than 1 to 1½ minutes it is usually unable to resume myocardial contraction even though it may be successfully defibrillated

This study was based on these observations and the clinical impression that ventricular defibrillation with DC countershock is also more difficult with increasing duration of ventricular fibrillation The results demonstrate that 12 8 cm diameter paddle electrodes are more effective than 8 0 cm diameter paddle electrodes in transthoracic electrical defibrillation of canine hearts

The reason for the increased defibrillation effectiveness of the larger diameter paddle electrodes is unclear, but may be related to the decrease in the transthoracic impedance to DC countershock with larger size paddle electrodes [3] The transthoracic impedance encountered with the 12 8 cm electrodes was 44 9 ± 6 6 ohms whereas that encountered with the 8 0 cm electrodes was 66 5 ± 10 6 ohms As illustrated in Fig 2, when the same amount of energy is discharged from a DC defibrillator into varying resistive loads the delivered peak current increases with decreasing resistance or impedance Since it has been shown that a minimal current per body weight is necessary for transthoracic ventricular defibrillation in subjects ranging in weight from 2 3 to 340 kilograms,[5] any measure which lowers transthoracic impedance to DC countershock such as using the correct paddle electrode-chest wall interface or using larger diameter electrode paddles,[3] should enhance defibrillation effectiveness However because of decreasing current density with increasing paddle electrode size there is probably an optional electrode size above which defibrillation effectiveness will decrease This study shows that for subjects in the weight range of 13 to 31 kilograms 12 8 cm paddle electrodes are more effective than 8 0 cm diameter electrodes

Summary

Myocardial necrosis from repeated direct current defibrillation discharges is less when the same stored energy is delivered by paddle electrodes that are larger than those presently available on the majority of commercial defibrillators The present study was undertaken to determine if the larger 12 8 cm diameter paddle electrodes are as effective as the standard 8 0 cm diameter paddle electrodes in defibrillation Ventricular fibrillation (VF) was induced in 45 dogs and each was allowed to remain in ventricular fibrillation for progressively longer time intervals before defibrillation was attempted With the 12 8 cm diameter paddle electrodes, the longest duration of VF successfully terminated was 1 22 ± 1 05 minutes whereas this duration was 0 56 ± 0 61 minutes when the 8 0 cm paddle electrodes were used (p < 0 02) Ventricular fibrillation was terminated during the first minute with the 12 8 cm diameter electrode in 88 per cent of trials as compared with a 71 per cent success rate with 8 0 cm diameter paddle electrodes (p < 0 04) When the success rates during the first minute of VF for both sizes of paddle electrodes were plotted against the measured transthoracic impedance a high correlation coefficient (r = −0 94) was found

This study suggests that 12 8 cm diameter paddle electrodes are more effective for defibrilla

Table I Histological features defining the age of myocardial lesions

Hours (< 48 hr)	Days (2 14 days)	Weeks (2 8 wk)	Months (2 12 mo)	Years (> 1 yr)
Myocardium				
Thin wavy muscle cells	Peak inflammatory cell response	Progressive granulation tissue ingrowth re moval of necrotic muscle and replace ment fibrosis	Replacement fibrosis with progressive de crease in vascularity and residual pig mented macrophages	Mature replacement fi brosis
Contraction band necrosis	Prominent macro phages and connec tive tissue cells			
Karyolysis				
Early inflammatory cell response	Muscle cell regenera tive attempts			
Endocardium				
Acute inflammation	Connective tissue cell proliferation	Collagen and elastic fi bers appear	Developing endocardial fibroelastosis	Mature endocardial fi broelastosis

stains. The only myocardial lesions excluded from review were those related to cardiac surgery which are the subject of a separate study [1]

Each myocardial lesion was assigned to an age category according to the histological features listed in Table I The age categories—hours (up to 48 hours) days (2 to 14 days) weeks (2 to 8 weeks) months (2 to 12 months) and years (over 1 year)—were chosen because it was felt possible to accurately assign each lesion to its appropriate category on histological features alone The recently described thin wavy muscle cell change [2] proved of particular value in assessing early myocardial lesions Contraction band *necrosis* also called myofibrillar degeneration is a distinct form of cardiac muscle cell injury which occurs following reperfusion of transiently unperfused myocardium Areas of contraction band necrosis generally undergo a sequence of inflam matory and reparative changes similar to that seen with coagulation necrosis The endocar dium also undergoes a sequence of changes lead ing with larger lesions to endocardial fibroelas tosis over the area of myocardial necrosis Assessment of the stages of endocardial change provided additional information on lesion age and was particularly helpful with the older injuries

Thrombus organization within the coronary vessels progressed through the typical stages generally described Early thrombi consisted of a meshwork of platelets red cells and white cells entrapped in fibrin often with recognizable lines of Zahn This type of histology characterized thrombi less than 48 hours of age Subsequent changes included a condensation of the cellular elements such that the thrombi took on a more homogenous compact appearance often associated with minimal retraction from the intimal surface and the formation of small slitlike spaces At about 5 to 6 days of age spindle shaped mesenchymal type cells could be seen within the internal portions of the thrombi and from 7 to 12 days of age clear cut evidence of small vessel proliferation often developing most prominently near the intimal attachment of the thrombus Variable degrees of hemosiderin deposition and focal liquefactive necrosis could be seen in thrombi of this age Thrombi weeks in age were characterized by multiple small vascular chan nels of recanalization with progressively few er—but larger—channels forming as organization progressed to months in age By this time the thrombotic material was indistinguishably incor porated into the vessel wall with an appearance identical to that of an atherosclerotic plaque In thrombi which were years in age and not com pletely occlusive usually only a single or double channel of recanalization was present

For each myocardial lesion found an attempt was made to identify any associated coronary lesion The postmortem arteriograms were reviewed and compared by gross examination to the major epicardial coronary arteries which were transversely sectioned at 2 to 3 mm intervals Blocks containing coronary artery lesions were removed for histological study employing hema toxylin and eosin and elastic stains routinely and when indicated were stained with Masson s tri

The relationship between coronary artery lesions and myocardial infarcts Ulceration of atherosclerotic plaques precipitating coronary thrombosis

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Despite numerous studies no general agreement on the cause effect relationship between coronary artery lesions and myocardial infarcts has been achieved[1-9] Within the past several years a few investigations have independently arrived at the conclusion that focal atherosclerotic ulcerations or ruptures precipitate coronary thromboses and are antecedent and causally related to myocardial infarction[1-30] A separate school of thought has proposed that coronary thrombosis occurs secondarily and as a result of myocardial infarction[31-34] Discrepancies and variations in definition, methodology, and interpretation have been the subject of recent editorials and symposia[35-39]

In view of the therapeutic and prophylactic importance of an understanding of the pathogenesis of myocardial infarction and because of the controversy still expressed with regard to this problem we have undertaken a study of the nature and frequency of the coronary artery lesions associated with myocardial injuries in a large group of patients examined at autopsy The pathological nature of each myocardial lesion defined simply as an injury at least 3 cm in one dimension was studied and the presence and nature of an associated vascular lesion then determined It was felt that such an approach would avoid prejudgment on the question of infarct–coronary lesion interrelationships Our findings revealed a high association between coronary lesions and myocardial lesions and furthermore strongly suggested that endothelial injuries in the form of plaque ulcerations erosions, or plaque disruptions underlay the vast majority of coronary thromboses and most likely provided the nidus for thrombus formation Acute occlusive coronary lesions appeared to antecede and precipitate the majority of myocardial infarcts

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Materials and methods

The clinical and pathological features of 680 patients autopsied at The Johns Hopkins Hospital whose hearts had been studied in the Myocardial Infarction Research Unit Pathology Laboratory from December 1967, through July, 1974 were reviewed These hearts had been selected for special study from the 3 920 autopsies performed during that period because of known or suspected cardiovascular or pulmonary disease The hearts were prepared by coronary arteriography with a barium gelatin pigment mass and were fixed in distension prior to sectioning transversely Photographs stereoscopic radiographs in two planes and histologic sections were prepared from each specimen

A myocardial lesion was defined as an area of destruction of myocardium that had at least one dimension 3 cm or greater Lesions were designated transmural if they involved more than half the thickness of the myocardium and subendocardial when involving less than half of the inner portion of the myocardial wall Portions of each myocardial lesion were removed for histological study with hematoxylin and eosin and Verhoeff-van Gieson or aldehyde fuchsin elastic

Table I Histological features defining the age of myocardial lesions

Hours (< 48 hr)	*Days (2-14 days)*	*Weeks (2-8 wk)*	*Months (2-12 mo)*	*Years (> 1 yr)*
Myocardium				
Thin wavy muscle cells	Peak inflammatory cell response	Progressive granulation tissue ingrowth, removal of necrotic muscle and replacement fibrosis	Replacement fibrosis with progressive decrease in vascularity and residual pigmented macrophages	Mature replacement fibrosis
Contraction band necrosis	Prominent macrophages and connective tissue cells			
Karyolysis				
Early inflammatory cell response	Muscle cell regenerative attempts			
Endocardium				
Acute inflammation	Connective tissue cell proliferation	Collagen and elastic fibers appear	Developing endocardial fibroelastosis	Mature endocardial fibroelastosis

stains The only myocardial lesions excluded from review were those related to cardiac surgery which are the subject of a separate study [11]

Each myocardial lesion was assigned to an age category according to the histological features listed in Table I The age categories—hours (up to 48 hours) days (2 to 14 days) weeks (2 to 8 weeks) months (2 to 12 months) and years (over 1 year)—were chosen because it was felt possible to accurately assign each lesion to its appropriate category on histological features alone The recently described thin wavy muscle cell change proved of particular value in assessing early myocardial lesions Contraction band necrosis also called myofibrillar degeneration is a distinct form of cardiac muscle cell injury which occurs following reperfusion of transiently unperfused myocardium [3,4] Areas of contraction band necrosis generally undergo a sequence of inflammatory and reparative changes similar to that seen with coagulation necrosis [5] The endocardium also undergoes a sequence of changes leading with larger lesions to endocardial fibroelastosis over the area of myocardial necrosis Assessment of the stages of endocardial change provided additional information on lesion age and was particularly helpful with the older injuries

Thrombus organization within the coronary vessels progressed through the typical stages generally described [2] Early thrombi consisted of a meshwork of platelets red cells and white cells entrapped in fibrin often with recognizable lines of Zahn This type of histology characterized thrombi less than 48 hours of age Subsequent changes included a condensation of the cellular elements such that the thrombi took on a more homogenous compact appearance often associated with minimal retraction from the intimal surface and the formation of small slitlike spaces At about 5 to 6 days of age spindle shaped mesenchymal type cells could be seen within the internal portions of the thrombi and from 7 to 12 days of age clear cut evidence of small vessel proliferation often developing most prominently near the intimal attachment of the thrombus Variable degrees of hemosiderin deposition and focal liquefactive necrosis could be seen in thrombi of this age Thrombi weeks in age were characterized by multiple small vascular channels of recanalization with progressively fewer—but larger—channels forming as organization progressed to months in age By this time the thrombotic material was indistinguishably incorporated into the vessel wall with an appearance identical to that of an atherosclerotic plaque In thrombi which were years in age and not completely occlusive usually only a single or double channel of recanalization was present

For each myocardial lesion found an attempt was made to identify any associated coronary lesion The postmortem arteriograms were reviewed and compared by gross examination to the major epicardial coronary arteries which were transversely sectioned at 2 to 3 mm intervals Blocks containing coronary artery lesions were removed for histological study employing hematoxylin and eosin and elastic stains routinely and when indicated were stained with Masson s tri

The relationship between coronary artery lesions and myocardial infarcts Ulceration of atherosclerotic plaques precipitating coronary thrombosis

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Despite numerous studies no general agreement on the cause effect relationship between coronary artery lesions and myocardial infarcts has been achieved [1-20] Within the past several years a few investigations have independently arrived at the conclusion that focal atherosclerotic ulcerations or ruptures precipitate coronary thromboses and are antecedent and causally related to myocardial infarction [21-30] A separate school of thought has proposed that coronary thrombosis occurs secondarily and as a result of myocardial infarction [31-34] Discrepancies and variations in definition methodology and interpretation have been the subject of recent editorials and symposia [35-39]

In view of the therapeutic and prophylactic importance of an understanding of the pathogenesis of myocardial infarction, and because of the controversy still expressed with regard to this problem we have undertaken a study of the nature and frequency of the coronary artery lesions associated with myocardial injuries in a large group of patients examined at autopsy The pathological nature of each myocardial lesion defined simply as an injury at least 3 cm in one dimension, was studied and the presence and nature of an associated vascular lesion then determined It was felt that such an approach would avoid prejudgment on the question of infarct–coronary lesion interrelationships Our findings revealed a high association between coronary lesions and myocardial lesions and furthermore strongly suggested that endothelial injuries in the form of plaque ulcerations erosions, or plaque disruptions underlay the vast majority of coronary thromboses and most likely provided the nidus for thrombus formation Acute occlusive coronary lesions appeared to antecede and precipitate the majority of myocardial infarcts

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Materials and methods

The clinical and pathological features of 680 patients autopsied at The Johns Hopkins Hospital whose hearts had been studied in the Myocardial Infarction Research Unit Pathology Laboratory from December, 1967, through July, 1974, were reviewed These hearts had been selected for special study from the 3 920 autopsies performed during that period because of known or suspected cardiovascular or pulmonary disease The hearts were prepared by coronary arteriography with a barium gelatin pigment mass and were fixed in distension prior to sectioning transversely [40] Photographs stereoscopic radiographs in two planes and histologic sections were prepared from each specimen

A myocardial lesion was defined as an area of destruction of myocardium that had at least one dimension 3 cm or greater Lesions were designated transmural if they involved more than half the thickness of the myocardium and subendocardial when involving less than half of the inner portion of the myocardial wall Portions of each myocardial lesion were removed for histological study with hematoxylin and eosin and Verhoeff–van Gieson or aldehyde fuchsin elastic

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Fig 2 A Transverse section of a coronary artery with the lumen occluded by thrombus. Focus of endothelial erosion is present at the lower portion of the lumen (arrow) (Hematoxylin and eosin ×30) B Closeup of point of erosion of the atherosclerotic plaque Admixture of plaque thrombu and inflammatory cells is shown (Hematoxylin and eosin ×200)



Fig 3 A Transverse section of a coronary artery with the lumen (top) and an empty atherosclerotı plaque (below) filled with dark staining injection mass The remnants of the fibrous cap of the emptied plaque protrude into the lumen and have associated nonocclusive thrombus depo its on their surfaces (Hematoxylin and eosin ×25) B An intramyocardial coronary artery within an area of myocardial necrosis occluded by an embolus of admixed atheromatous plaque debris and thrombus. The coronary lesion in this instance was similar to that shown in A (Hematoxylin and eosin ×125)

necrosis was confined to the distribution of the respective vessel in each case Twelve lesions were transmural and five were subendocardial in nature In every instance occlusive or partially occlusive thrombus was present within the vessel lumen in the region of the stenosing atherosclerotic plaque Seven lesions were totally occlusive as judged by postmortem angiograms six were 90 to 99 per cent occlusive two were 50 to 90 per cent occlusive and two were less than 50 per cent occluded. Serial sectioning of these thrombosed coronary segments revealed an underlying intimal ulceration (Fig 1) plaque erosion (Fig 2) or disrupted or ruptured plaque (Fig 3) in 16 of 17 cases (94 per cent) Thrombotic material was intimately associated with the respective foci of ulceration or erosion overlying the plaques and in instances where the plaque was ruptured throm

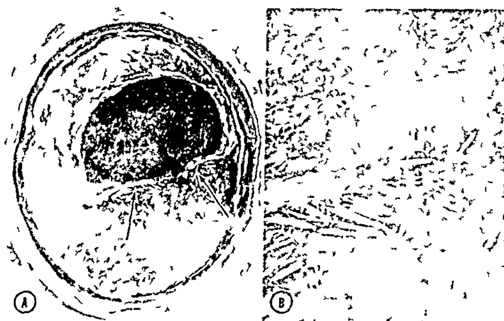


Fig 1 *A* Transverse section of a coronary artery occluded by thrombus arising at an area of ulceration on the fibrous cap of the atheroma Note frayed edges of the damaged endothelial surface (arrows) (Hematoxylin and eosin ×25) *B* Point of plaque ulceration showing intimate admixture of atheromatous plaque content (below) and lumenal thrombus (above) Region shown is area between arrows on the left (Hematoxylin and eosin ×75)

Table II Distribution of myocardial lesions

	Hours (< 48 hr)	*Days (2 14 days)*	*Weeks (2 8 wk)*	*Months (2 12 mo)*	*Years (> 1 yr)*	*Total*
Atherosclerotic	17	52	21	63	265	418
Embolic	3	5	5	6	36	55
Hypoperfusion	7	9	2	0	0	18
Other	1	0	0	1	1	3
Total myocardial lesions	28	66	28	70	302	494

chrome and phosphotungstic acid-hematoxylin Serial sections were made of the artery blocks when necessary for delineation of the lesion and when the coronary lesion was recent (from less than one day to several weeks of age) Almost all blocks were serially sectioned transversely a few were sectioned longitudinally

Postmortem angiographic scoring was tabulated in each case based on a method utilized clinically [48] Each case was reviewed for the clinical and pathological features of the cardiac problems in particular, the clinical age of myocardial lesions was compared to the pathological dating The gross microscopic and angiographic findings from the postmortem study of the heart were interpreted in light of the clinical information of each patient

Results

A total of 494 myocardial lesions as previously defined were identified—in 287 hearts among the 680 reviewed—and included in this study Myocardial lesions were dated and placed into age categories on the basis of histopathological changes as outlined in Table I Within the age groupings the associated coronary lesions were found to fit into four categories (1) atherosclerotic coronary lesions, (2) embolic coronary lesions (3) no coronary lesions but associated with clinical events causing coronary hypoperfusion and (4) miscellaneous or other coronary lesions The breakdown into these subgroupings of coronary lesions for each age group of myocardial lesions is summarized in Table II

Group A Myocardial lesions hours old Twenty eight myocardial lesions were pathologically less than 48 hours of age

Atherosclerotic Seventeen cases were associated with a severe atherosclerotic coronary lesion situated within an extramural coronary segment several centimeters (1 to 2 cm) proximal to infarcted myocardium The area of tissue



Fig 5 *A* Transverse section of an occluded coronary artery The lumen filled with fresh thrombus is in the upper left An atheromatous plaque with ulceration of its thin fibrous cap is shown by the arrows (Hematoxylin and eosin ×50) *B* An area near the middle arrow of the left figure showing that the fibrin deposit on the plaque surface is older than the 9 hour old myocardial infarct in the distribution of the occluded vessel (Hematoxylin and eosin ×200)

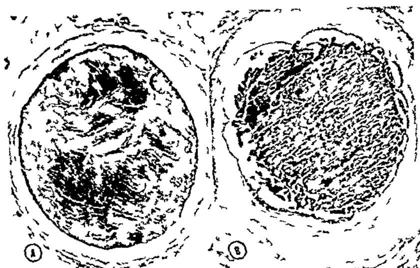


Fig 6 *A* Fresh thromboembolus occluding the coronary artery lumen *B* Older thromboembolus showing separation from the coronary artery wall and recanalization (Both *A* and *B* Hematoxylin and eosin ×40)

cases and over 95 per cent occlusive in one Underlying atherosclerotic coronary disease within the embolized segments was mild in each case as was coronary artery disease in these patients in general A source of embolization was identified in each one arose from mural thrombus associated with an older infarct another from atrial thrombus in a setting of atrial fibrillation and the third from a catheter tip during cardiac catheterization Two myocardial lesions were transmural and the third subendocardial

Hypoperfusion Seven myocardial lesions in this group were unassociated with an acute coronary lesion All were subendocardial in location Myocardial necrosis was not confined to the distribution of a single coronary vessel but rather overlapped the regions perfused by two or more coronary arteries Tissue necrosis was similar to that found in the previous cases (Fig 7) with the exception of more frequent necrosis of the contraction band type (Fig 8)

In every case a clinical event which could

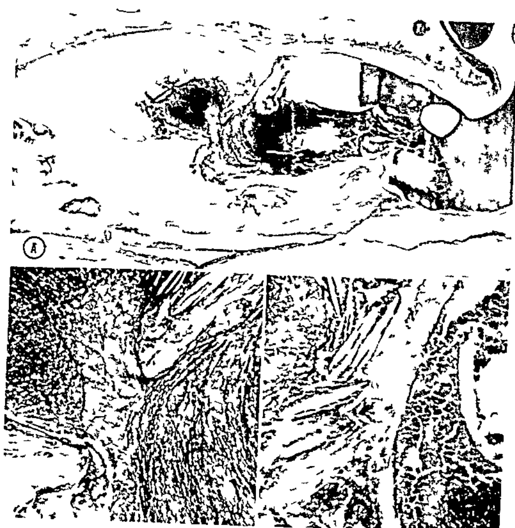


Fig 4 *A* Longitudinal section of an occluded coronary artery segment Dark staining injection mass fills the lumen of the proximal portion on the right and in the center on the left the lumen is obliterated by atheroma and overlying thrombus The thrombus is attached to an ulceration in the fibrous cap of the atherosclerotic plaque (Phosphotungstic acid hematoxylin ×30) *B* The ulcer in the fibrous cap of the atheroma showing admixture of thrombus and plaque debris (Phosphotungstic acid hematoxylin ×90) *C* Intact fibrous cap of the atheroma in a serial section 120μ removed from the section shown on the left (Phosphotungstic acid hematoxylin ×90)

botic material was observed along the edges of the torn fibrous caps Atherosclerotic debris was intimately admixed with thrombus in several instances but more often lay immediately beneath and juxtaposed to thrombus at the site of plaque ulceration

The endothelial ulcerations were focal in nature and often appeared in only two or three transverse coronary sections examined at 120 μ intervals (Fig 4)

Thrombi in these cases consisted of conglutinated red cells, white cells and platelets enmeshed in fibrin Recognizable lines of Zahn were a regular feature less often pure platelet aggregates were identified

The underlying atherosclerotic lesions were usually soft in nature made up of amorphous pultaceous debris, cholesterol lipid laden macrophages, and associated with varying degrees of inflammation Intramural hemorrhage was inconstant and of variable degree The intimal layer overlying these plaques in areas free of ulceration was usually thinned and often appeared to be eroded along its under surface This fraying was more prominent near the periphery of the endothelial ulcerations and at the edges of torn fibrous caps The common feature of all these lesions was an altered intimal surface underlying lumenal thrombosis In six instances the thrombus was clearly older than the age of the associated myocardial lesion (Fig 5)

In the single case in which endothelial ulceration was not identified thrombus and a related atherosclerotic plaque similar to those just described were present

Embolic Three myocardial lesions were associated with coronary artery thromboemboli (Fig 6) The emboli were completely occlusive in two

myocardial necrosis throughout the distribution of the left coronary system Platelet aggregates were adherent to the exposed surfaces of the disrupted plaque and plaque contents were lodged within the coronary lumen

Group B Myocardial lesions days old Sixty six myocardial lesions were 2 to 14 days of age pathologically

Atherosclerotic Fifty two myocardial lesions were associated with a severe atherosclerotic coronary narrowing situated several centimeters proximal to the infarcted region of myocardium All 52 lesions were confined to the distribution of the respective narrowed vessel Thirty seven of the 52 myocardial lesions were transmural and 15 subendocardial Totally occlusive or partially occlusive thrombus was present in 50 of 52 cases within the coronary lumen near the site of maximal narrowing

Of 52 coronary lesions 32 were totally occlusive by radiographic and histological examination fourteen were 90 to 99 per cent occlusive five were 50 to 90 per cent occlusive and one was less than 50 per cent occlusive In 48 of the 52 cases (92 per cent) serial sectioning of the thrombosed coronary segments revealed endothelial ulceration erosions or disruptions overlying the atherosclerotic plaques causing stenosis (Figure 9) Thrombus was adherent at these points of wall injury most often to underlying exposed atherosclerotic debris. In instances where fibrous caps overlying plaques were more severely disrupted thrombus was adherent to their free edges and in addition more intimately admixed with plaque contents Points of ulceration as in the previous group were focal in nature most often extending over a length of less than 150 microns Sections examined immediately distal or proximal to points of ulceration often revealed attenuated fibrous caps suggesting imminent disruption A macrophage infiltration was frequent along the undersurface of the thinned fibrous caps The majority of ulcerations were present over soft atheromata

Thrombus was usually present over a distance of 0 5 to several centimeters extending on either side of the endothelial ulceration In four cases thrombus was scant and appeared adherent to the vessel wall only at the points of recent intimal injury Recanalization may have eroded portions away in these instances

The coronary lesions in the days age group were characterized by early stages of organization Up to 6 to 7 days of age these thrombi were similar histologically to those hours of age with the exception that thrombotic material was denser and had taken on a harder hyaline look Leukocytes were fragmented and disintegrated in all cases At approximately 1 week of age macrophage infiltration fibroblastic and mesenchymal proliferation and early capillary penetration were recognized The latter became most prominent at 10 to 14 days when endothelial cell

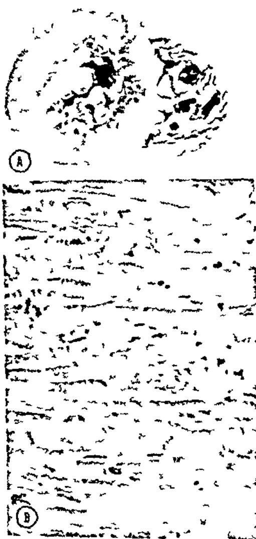


Fig 8 A Transverse section of cardiac ventricles with patchy subendocardial necrosis of the left ventricle not confined to the distribution of a single coronary artery Note the darker hemorrhagic appearance of the involved areas which is characteristic of hypoperfusion necrosis There were no acute coronary artery lesions, but the patient had suffered an episode of fibrillation 2 days before death *B* Contraction band necrosis with marked congestion of small blood vessels from an area of hypoperfusion necrosis. (Hematoxylin and eosin ×400)

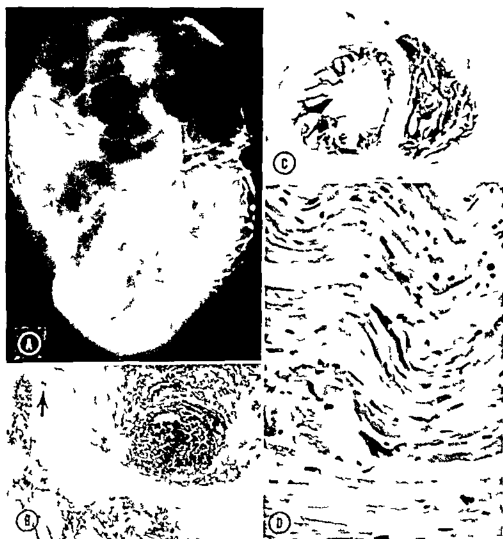


Fig 7 *A* Postmortem coronary arteriogram demonstrating nonfilling of the left anterior descending coronary artery (viewed anteriorly with atria above and ventricles below) Note the dilatation of the apical portion of the left ventricular cavity *B* Transverse section of the left anterior descending coronary artery at the point of occlusion The lumen is filled with fresh thrombus but the thrombus at the point of atherosclerotic plaque ulceration (arrow) is histologically older (Hematoxylin and eosin ×40) *C* Transverse section of the cardiac ventricles Note the slight thinning paler color and confinement to the distribution of the left anterior descending coronary artery of the infarcted anteroseptal left ventricular myocardium *D* Thin wavy muscle cells and acute inflammatory cells in the area of myocardial infarct which is 26 hours old Note the surviving muscle cells at the bottom (Hematoxylin and eosin ×400)

account for coronary hypoperfusion was present Three of seven patients had severe generalized coronary artery disease and all seven had at least one 90 per cent or greater narrowing within a segment of a large extramural coronary artery

Three of these patients died within 48 hours of sudden cardiorespiratory arrests one arrest occurring during insertion of a central venous pressure catheter A third patient had calcific aortic stenosis with a known gradient by previous catheterization study of 75 mm and also died suddenly One patient developed atrial fibrillation during cardiac catheterization and died less than 2 days later with patchy circumferential subendocardial necrosis and severe stenosis (90 per cent) of his left main coronary artery

The sixth patient in this group developed A V dissociation on the third day following an acute myocardial infarct suffered a cardiorespiratory arrest was resuscitated, and died 1 day later Very fresh patchy necrosis was present subendocardially in addition to a discrete transmural anteroseptal infarct of approximately 4 days of age The final patient in this group who had long standing diabetes was hypotensive and had diabetic ketoacidosis preterminally

Other One myocardial lesion did not fit into the three categories above This patient had a severe narrowing (90 per cent) of his left main coronary artery which was disrupted at the time of cardiac catheterization He died less than 12 hours later and showed very early transmural

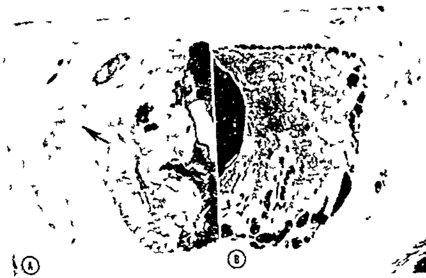


Fig 10 *A* Section of partially occluded coronary artery supplying an area of myocardial necrosis ? weeks of age The torn edge of fibrous cap of an ulcerated atheromatous plaque is shown (arrow) embedded in organizing thrombus (Hematoxylin and eosin ×50) *B* Multiple channels of recanalization filled with dark injection mass in an organizing admixture of thrombus and atheromatous plaque debris The artery supplied an area of myocardium with an infarct 5 weeks old (Hematoxylin and eosin ×40)

Three patients had prolonged bouts of refractory hypotension 2 to 14 days prior to death Shock followed a cerebrovascular accident in one instance In another cardiogenic shock developed 10 days following an acute myocardial infarct This patient died 4 days later and at autopsy the heart showed a discrete transmural infarct approximately 2 weeks of age and more recent subendocardial necrosis 3 to 4 days old In the third patient hypotension developed in the setting of several old myocardial infarcts and a long history of progressive congestive heart failure The patient died in pulmonary edema refractory to medical therapy and at autopsy the heart showed recent multicentric subendocardial necrosis and two old myocardial infarcts with associated coronary lesions

In one case atrial fibrillation developed 1 week prior to death in a patient with an old anterior infarct and progressive congestive heart failure Circumferential subendocardial necrosis 7 days old was identified at autopsy The last patient became hypotensive during a cardiac catheterization procedure and shortly thereafter showed evidence of acute anterior infarction He died 3 days later with circumferential subendocardial necrosis and was found to have a severe atherosclerotic lesion of the left main coronary artery without evidence of intimal injury or thrombosis

Myocardial necrosis in this group was similar to that noted in the group with atherosclerotic thrombotic coronary lesions with the exception that necrosis of the contraction band type was found with much greater frequency

Group C Myocardial lesions weeks old Twenty-eight myocardial lesions were 2 to 8 weeks of age

Atherosclerotic Twenty one lesions within this group were associated with partial or total thrombotic occlusions within severely narrowed atherosclerotic coronary segments The coronary lesions were situated 1 to 2 cm proximal to infarcted myocardium which lay within the flow distribution of the respective diseased coronary segments in each case Five of 21 coronary lesions were totally occluded as judged by postmortem angiograms and histology 15 were 90 to 99 per cent occluded and one was 75 per cent occluded Nine myocardial lesions were transmural and 12 were subendocardial

In 17 of the 21 cases (80 per cent) a focal plaque ulceration erosion or endothelial surface disruption was identified within the partially or totally thrombosed coronary segments (Fig 10) The general pathological features of these lesions were similar to those which have been previously described among the atherosclerotic subgroups Organization not only within the lumenal thrombus but also at the plaque thrombus inter



Fig 9 *A* Section of coronary artery totally occluded with admixed thrombus atheromatous plaque debris and fibrous cap (arrow) from the vessel supplying an area of myocardial necrosis 5 days old (Hematoxylin and eosin ×30) The inset shows the intimate relationship of fibrotic cap (at arrow in the overview) thrombus and plaque debris (Hematoxylin and eosin ×125) *B* Section of partially occluded coronary artery supplying an area of myocardial necrosis 10 days old Injection mass is darkly stained The fibrous cap of the atherosclerotic plaque is extensively ulcerated and the exposed pultaceous debris is admixed with thrombus. (Hematoxylin and eosin ×25) The inset shows the torn edge of the fibrous cap (at arrow in overview) and admixed thrombus and plaqu material (Hematoxylin and eosin ×125)

proliferation became more apparent Other areas of fresher laminated thrombus were present over older organizing portions of the thrombus In no case could it be stated with certainty that the oldest observed portion of the thrombus was younger than that of the myocardial lesion On the contrary, in four cases portions of the thrombus clearly antedated the myocardial lesion

In the remaining four cases in which a myocardial lesion and an associated severe atherosclerotic lesion were present, a focal plaque ulceration was not identified in the coronary sections examined Coronary thrombi were found in two cases and no coronary lesion was identified in the other two

Embolic Five myocardial lesions were accounted for by coronary embolization Two were subendocardial and three transmural Embolic material was identified in each and in each case the coronary vasculature was otherwise radiographically and histologically normal Three patients had endocarditis One had acute bacterial endocarditis involving the aortic valve associated with an occlusive septic coronary embolus and another had endocarditis superimposed on a prosthetic aortic valve and an embolic related myocardial abscess The third patient had marantic endocarditis of the mitral valve and a bland occlusive coronary embolus identical to material adherent to the valve leaflets

The remaining two patients had small thromboemboli within distal intramural coronary branches which were otherwise normal Their source could not be identified with certainty but they probably were of atrial origin

Hypoperfusion Nine myocardial lesions were unassociated with an acute coronary lesion but were accounted for by various clinical problems resulting in generalized and/or coronary hypoperfusion All but one were subendocardial and six of nine involved overlapping extramural coronary distributions Four of these patients had cardiorespiratory arrests were resuscitated successfully but died 2 to 14 days later One arrest followed a cerebrovascular accident and a second occurred suddenly during a routine blood drawing procedure The other two patients arrested unexpectedly and without explanation Three of these patients had mild coronary artery disease and patchy circumferential necrosis the fourth had moderate coronary disease, an old infarct and coronary occlusion and recent necrosis at the periphery of this old infarct

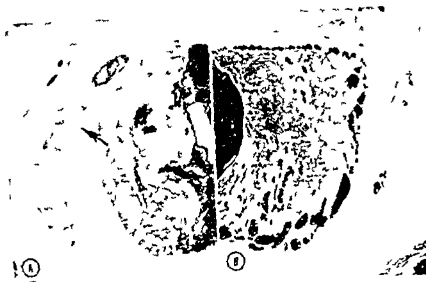


Fig 10 A Section of partially occluded coronary artery supplying an area of myocardial necrosis 2 weeks of age The torn edge of fibrous cap of an ulcerated atheromatous plaque is shown (arrow) embedded in organizing thrombus (Hematoxylin and eosin ×50) B Multiple channels of recanalization filled with dark injection mass in an organizing admixture of thrombus and atheromatous plaque debris The artery supplied an area of myocardium with an infarct 5 weeks old (Hematoxylin and eosin ×40)

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Fig 11 *A* Multiple channels of recanalization in organizing thrombus in the lumen of a coronary artery An endothelial injury could not be identified The myocardium in the distribution of this vessel had necrosis 3 months old (Masson ×40) *B* Multiple small channels of recanalization in organized thrombus occluding the lumen of a coronary artery with an area of myocardial infarction years old in its distribution Note what may represent the torn edges of an ulcerated atherosclerotic plaque at the arrows (Hematoxylin and eosin ×40)

face was frequent and rendered it difficult in several instances to identify for certain endothelial ulcerations

Recanalization was present in 16 of 21 thrombosed segments however the degree varied tremendously from case to case Early recanalization was characterized by multiple small endothelial lined channels coursing sinuously in some cases through edematous somewhat myxomatous thrombus material Hemosiderin deposition and inflammation were present in variable amounts The older lesions in this group showed a tendency toward fewer and larger channels of recanalization

In four of the 21 atherosclerotic thrombosed segments a focal area of endothelial injury or ulceration could not be identified with certainty These lesions were 7, 6, 4 and 3 weeks of age and although in other lesions of comparable age intimal ulcerations could be appreciated in this group of four organization of thrombus at the plaque thrombus interface obscured the evidence of any precipitating lesion

Embolic Five myocardial lesions in this group were thought to be the result of coronary embolization Three were transmural and two subendocardial In all five patients coronary artery disease was mild or negligible Emboli at various stages of organization were identified within the coronary vessels in each of the five cases In two cases the source of embolization was marantic endocarditis and in another thrombotic material attached to an aortic valve prosthesis A fourth patient had systemic lupus erythematosus, a widely patent foreamen ovale, and an occlusive thromboembolus lodged in an otherwise normal distal left anterior descending coronary artery The fifth patient had a partially occlusive thromboembolus in the distal intramural left anterior descending coronary artery but its source was not identified

Hypoperfusion In two cases in this group myocardial lesions were not accounted for by a recent coronary event Both were subendocardial One patient experienced a period of prolonged shock following pulmonary thromboembolism 3 weeks prior to death At autopsy his heart showed subendocardial necrosis overlapping several extramural coronary distributions The second patient died following a 1 month hospitalization for congestive heart failure and pneumonia He was intermittently hypotensive during his course and at autopsy was found to have subendocardial necrosis approximately 3 weeks old, peripheral to two old myocardial infarcts In the two above cases coronary artery disease was graded moder

ate to severe Myocardial necrosis in these few cases was similar to that seen in the atherosclerotic subgroup

Group D Myocardial lesions months old Seventy myocardial lesions in this study were 2 to 12 months of age pathologically

Atherosclerotic In 63 of the above cases a severe atherosclerotic stenosis or occlusion was present in a proximal coronary segment serving the region of infarction. Twenty one myocardial lesions were transmural and the remainder subendocardial Twenty three coronary lesions were completely occluded as judged by postmortem angiogram and histologic study 34 were 90 to 99 per cent occluded and six were 50 to 90 per cent occluded Among the 40 coronary lesions which were not totally occluded recanalization was demonstrated histologically in transverse coronary sections in 37 In only three cases within this subgroup was evidence of recanalization of previous thrombosis lacking

Pathologically lumenal recanalization consisted of multiple (two or more) endothelial lined channels coursing through organizing thrombus (Fig 11) Most of the central thrombotic debris at this stage was indistinguishable from the atherosclerotic changes seen in the coronary walls Macrophage infiltration focal hemorrhage cholesterol deposition and lakes of hyaline material were all histologic features seen within the partially occluded coronary lumens Totally occluded lumens were histologically similar

Recognizable areas of endothelial injury i.e plaque ulceration erosion or disruption were difficult to recognize in coronary lesions of this age In only eight cases were such areas clearly identified histologically in transverse coronary sections There were in other coronaries however areas of previous endothelial injury within segments containing organizing lumenal thrombus At such sites a defect in a fibrous cap of an atherosclerotic plaque associated with a proliferation of small vessels communicating between the deeper portions of the plaque and the central organizing thrombus could be seen This vascularity was most pronounced at the focus of plaque discontinuity where presumably the original intimal injury occurred

For the most part in this group of myocardial lesions age related changes and distortion obscured plaque surface thrombus interfaces where areas of endothelial injury had been noted in fresher coronary lesions

Embolic Six myocardial lesions in this group were interpreted as resulting from coronary embolization In four cases coronary artery disease was negligible embolic material was demonstrated histologically within the coronary vessels distributing to the region of infarction and the source of embolization was identified The sources included thrombotic material from a valve prosthesis material embolized from an infected rheumatic mitral valve atrial thrombus in a patient in atrial fibrillation and mural thrombus in a patient with long standing congestive heart failure

In the other two cases the source of embolization was mural thrombus overlying previous old myocardial infarcts Each patient had a single year-old infarct and an associated coronary occlusion, atherosclerotic in nature More recent subendocardial infarcts months in age were present Identifiable embolic material was present in one within a distal coronary branch but was not found in the other

Other One myocardial lesion in this group subendocardial in nature was related to coronary arteritis in a patient with giant cell arteritis

Group E Myocardial lesions years old There were 302 myocardial lesions histologically greater than 1 year of age

Atherosclerotic A total of 265 myocardial lesions were associated with a severe atherosclerotic narrowing or occlusion within an extramural coronary distributing to the region of old infarction Of the myocardial lesions 67 were transmural and 198 were subendocardial There were 118 coronary lesions completely occluded as assessed by postmortem angiography and histologic study 111 were 90 to 99 per cent occluded 31 were 50 to 90 per cent occluded and one was less than 50 per cent occluded Within the group of 147 which were not totally occluded histological study of transverse coronary sections revealed lumenal recanalization in 133 Thus evidence for old partial or total occlusion was demonstrated in 251 of 265 or 95 per cent of the coronary lesions

Pathological features of recanalization within this group differed from the previous group (Fig 12) Most often only two or three well formed vascular channels coursed through the region of



Fig 12 Remnants of organized recanalized thrombi in the lumens of coronary arteries with myocardial infarcts years of age in the distribution of the vessels Definite evidence of atherosclerotic plaque ulceration cannot be found Injection mass stains black (Both *A* and *B* Hematoxylin and eosin *A* ×30 *B* ×20)

remote thrombosis Complex multichannel recanalization was seen less often Organized lumenal thrombus blended indistinguishably into the atherosclerotic vessel walls in a majority of cases In this group of older lesions recanalized channels sometimes showed elastic lamina formation and smooth muscle proliferation within newly formed vessel walls ' Calcification foci of inflammation, and dystrophic ossification were seen In exceptional cases what may have been a previous site of endothelial disruption could be distinguished At such foci remnants of a disrupted plaque cap could be seen with small vascular channels running between deeper portions of the mural plaque and more central regions of organizing thrombus

Although ghosts of what we interpreted as ancient plaque ulcerations or disruptions were sometimes noted interpretation regarding the nature and pathogenesis of lumenal thrombosis was impossible in lesions of this age

Embolic Thirty six myocardial lesions in this group were thought to be the result of coronary embolization Twenty three were transmural and 13 subendocardial In 32 cases associated coronary artery disease was negligible In 28 of the 36 cases the source of embolization was identified In 13 atrial thrombus was present which in eight cases was associated with long standing atrial fibrillation Nine patients had mural thrombus within their ventricular chambers usually associated with long standing congestive heart failure Five of nine were considered to have idiopathic myocardiopathies In four patients embolization was from thrombotic material on prosthetic valves and in two arose from inactive bacterial endocarditis

In the eight cases in which the source of embolization was not identified the coronary arteries were normal in each evidence of systemic embolization was present in three and the infarct distribution always related to a distal small intramural coronary branch

In 11 of the 28 cases in which the embolic source was identified and in five of eight cases in which the embolic source was not identified histological examination of the coronary vessel distributing to the region of old infarction revealed evidence of lumenal recanalization Pathologically these were recognized as webs or bands within the coronary lumens as eccentric pads of organized thrombotic material adherent to otherwise normal coronary vessel walls or as well organized thrombus with several well developed channels of recanalization

Other A single myocardial lesion in this age group transmural in nature, was the result of arteritic involvement of a coronary vessel in a patient with giant cell arteritis

Discussion

The results of the present study strongly suggest that intimal ulcerations erosions or ruptures of atheromatous plaques provide a nidus

for occlusive coronary artery thrombosis which precipitates *the overwhelming majority* of myocardial infarcts In this study 494 myocardial lesions measuring at least 3 cm in one dimension were *reviewed Myocardial* lesions ranged from areas of fresh necrosis to areas of remote replacement fibrosis The size of myocardial injury necessary for inclusion was comparable to that of other studies of myocardial infarction[2, 3] but was chosen particularly on the basis of studies by Mitchell and Schwartz[8] who showed two distinct size populations of cardiac lesions Those greater than *3 cm could be correlated directly* with severity of coronary artery disease and thus bore a relationship to ischemic heart disease Those smaller than 3 cm did not correlate with coronary artery disease but only with age

Of the 494 myocardial lesions studied 418 were associated with an extramural atherosclerotic coronary lesion 55 were associated with coronary embolization and three were associated with vessel wall injury from arteritis or cardiac catheterization Eighteen lesions were associated with clinical episodes of *hypoperfusion*

Within the group of 418 atherosclerotic *coronary lesions complete* occlusion (remote or fresh) or histological evidence of lumenal recanalization was present in 399 (96 per cent) Thus there was a high correlation between coronary lesions and myocardial lesions

In the present study particular heed was paid to the time course and histopathological evolu*tion of* coronary lesions Among all five age groups with atherosclerotic related myocardial infarcts *evidence of a coronary* lesion was documented in over 90 per cent of cases within each group (see Table II) Of 328 infarcts older than 2 months of age 311 (95 per cent) were found to have either occlusive or recanalized coronary lesions This percentage is in agreement with many studies [illegible] and at variance with *others* [illegible] Although such a high percentage strongly implicates a cause-effect relationship between *coronary lesions and* myocardial infarcts *the age-related histological* changes within these group obscured underlying pathogenetic mechanisms Indeed the pathological features seen within older organizing thrombi are indistinguishable from atherosclerotic changes as seen in the coronary walls This in fact could explain the *inability to recognize* evidence of a previous coronary lesion in 5 per cent of the cases recanalization with a resultant single lumen and surrounding organized thrombus is identical histologically to a narrowed atherosclerotic coronary vessel without previous occlusion

Within the group *of atherosclerotic related* infarcts less than 2 weeks *of age* a partially or totally occlusive *thrombus was present in 67 of 69* cases (97 per cent) In 64 of 69 *infarcts* (93 per *cent) injury to the endothelium overlying* atherosclerotic plaques was identified in the form of *ulcers, small* erosions or frank plaque disruptions Interface injuries such as these appeared to be the precipitating nidus *for thrombus* deposition and underlay the partially or totally occlusive coronary thrombus in each instance

The presence of such changes associated with coronary thrombus formation and myocardial infarction provides the strongest evidence that acute coronary lesions antecede and precipitate myocardial infarction In addition to *the histological* findings which show the focal ulcers and *endothelial injuries to be the central focus of* thrombosis ancillary findings provide additional *confirmatory evidence* Thrombus plaque debris *admixtures within the coronary* lumen and near the area of endothelial injury found in 17 of 69 (25 per cent) acute atherosclerotic coronary lesions in this study and thrombus plaque admixtures observed in distal coronary segments downstream from disrupted plaques and thrombosis noted in an additional four cases (6 per cent) can be explained only by coronary events which antecede thrombosis and myocardial infarction

Furthermore as noted in the previous descriptions of the acute arterial lesions in this study in no *instance could it* be said *with* certainty that the atherosclerotic ulceration thrombus complex was younger in age than its *associated infarct* On the contrary in 10 cases (14 per cent) focal areas of atherosclerotic thrombus admixtures were several days older than their associated myocardial infarcts usually in regions located within deep portions of the thrombus at the thrombus plaque ulceration interface This could be ascertained *with certainty* only when portions of the thrombi showed areas of capillary ingrowth and organization *and their respective* associated infarcts were definitely younger in age Serial section study of the coronaries involved is requisite for detection of the oldest portions of the thrombus

Beyond 2 weeks of age and *up to 2 months of*

Table III Histological features of atherosclerotic coronary artery lesions causing myocardial infarcts

	Hours (< 48 hr)	*Days* (2 14 days)	*Weeks* (2 8 wk)	*Months* (2 12 mo)	*Years* (> 1 yr)
Number	17	52	21	63	[illegible]
Thrombotic occlusion	17 (100%)	50 (96%)	21 (100%)	60 (95%)	[illegible]
Lumenal narrowing					
100%	7	32	5	23	118
90 99%	6	14	15	34	111
50 90%	2	5	1	6	31
< 50%	2	1	0	0	1
Atherosclerotic plaque ulceration	16 (94%)	48 (92%)	17 (80%)	8 (13%)	0
Ulceration	10	35	14	7	0
Ruptured cap	6	13	3	1	0
Plaque thrombus admixture	7	14	5	0	0
Portion of thrombus antedating myocardial lesion	6	4	0	0	0

age, although evidence of recent coronary thrombosis was detectable in each case, underlying interface injuries were more difficult to distinguish and were found in 17 of 21 (80 per cent) atherosclerosis related infarcts Of the four coronary thrombus lesions in which underlying endothelial injury could not be recognized histologically, one was less than 4 weeks of age and three were from 4 to 8 weeks of age Eight myocardial lesions in this group were 4 to 8 weeks of age and 13 were 2 to 4 weeks of age Thus underlying intimal injuries, usually ulcerations could be recognized in 12 of 13 cases (92 per cent) in the 2 to 4 week range One month of age was the time at which detection of underlying plaque lesions became difficult Beyond this time organization of coronary thrombi and their incorporation into the coronary walls obscured evidence of the precipitating lesions A summary of the pathological features of atherosclerotic coronary lesions of all ages is given in Table III

Plaque ulceration or endothelial injury as an underlying nidus for coronary thrombus has been appreciated for many years[50, 51] however not until recent studies by Constantinides[21] Friedman,[4] Chapman,[23, 27] [8] Friedman and Van den Bovenkamp[2] Bouch and Montgomery[6] Jorgensen and associates[25] and Sinapius,[29, 30] where serial section studies of acute coronary lesions have been undertaken has the frequency of such intimal alterations underlying acute thrombosis been appreciated Constantinides[21] in a series of 17 recent coronary thrombi found underlying plaque fissures in every case Chapman[27] found recent coronary thrombi in 278 of 292 acute transmural myocardial infarcts and in a separate study of 19 recent coronary thrombi he[?] found lumenal thrombus adherent to the torn intimal surface of atherosclerotic plaques in each case Friedman and Van den Bovenkamp observed fractures or ruptures of the intima beneath coronary lumenal thrombus in 39 of 40 cases In a study of 78 patients dying within 48 hours from the onset of cardiac ischemia Jorgensen and associates[?] noted acute coronary arterial lesions in 89 per cent of 44 cases with pathological fresh myocardial infarcts Lesions were described as ruptured plaques both with and without thrombosis, nonruptured but ulcerated plaques and in three cases intraplaque hemorrhage Bouch and Montgomery[6] studied 100 fatal cases of recent myocardial ischemia and observed 88 occlusive coronary lesions in which 71 were found to be associated with ruptured soft atheromatous plaques Our findings related to recent coronary artery lesions are similar to these and support the concept that ulcerative atherosclerotic lesions such as a nidus for coronary thrombosis

The sequence of events leading to endothelial ulceration and/or plaque disruption requires further study It is apparent that there is continuous change within mural plaques including hemorrhage macrophage activity, inflammation, and collagen and elastic tissue breakdown Such processes may erode beneath the plaque surface leading to fibrous cap attenuation and ultimate ulceration Intraplaque pressure changes related to multiple small hemorrhages and associated fluid accumulations might be additional contributing factors in this process Likewise, intralu

menal sheer forces over endothelial surfaces already somewhat attenuated may be important in the pathogenesis of intimal injury

The morphology of intimal injury is variable In the majority of cases in this study an intimal ulceration overlying a soft atheromatous plaque was the basic lesion found Superimposed on this were laminated layers of fibrin and thrombus of similar ages Most often these lesions were totally or almost completely occlusive In a small percentage of cases ulceration and adherent thrombus were present in association with an infarct but the coronary lumen was still patent radiographically and histologically In these cases varying degrees of recanalization had probably occurred subsequent to more significant occlusive thrombus formation Also found frequently were areas of endothelial erosion which were less broad based than the ulcers just described often more focal tending to occur over harder" atherosclerotic plaques containing little pultaceous material as well as over soft atheromas In addition to plaque ulcerations and erosion more flagrant plaque disruption with extrusion of plaque contents was found in a small number of cases In these circumstances torn fibrous caps thrombus and plaque debris were admixed at the site of coronary occlusion An unusual variation of this phenomenon was found in even fewer cases where rupture and subsequent extrusion of plaque contents occurred leaving only a shelled out mural plaque Thrombus adherent to the torn edges of the plaque and admixed with plaque debris downstream were evidence of the occurrence of a real antemortem event in these uncommon instances

Later stages of endothelial injury and coronary thrombosis were characterized by progressive organization which was usually recognizably older at the region of intimal injury at the plaque thrombus interface In remote coronary lesions this latter finding was the only evidence found in a few cases suggesting the nature of the original event Disrupted fibrous plaque caps associated with proliferations of small vessels running between central portions of the thrombus and deeper portions of the mural plaque were recognizable

It should be noted that plaque injuries as described above associated with partial or total thrombotic occlusions of coronary lumens were also found without associated myocardial lesions These were seen frequently but the precise incidence of their occurrence was not tabulated Thrombus in these instances was often recognized to be of varying ages suggesting repeated events of thrombus precipitation In a few cases this was associated with clinical preinfarction angina suggesting that recurrent thrombotic events at a single coronary site might provide the pathogenetic basis for the preinfarction syndrome This idea has also been suggested by others[29]

Likewise intramural plaque hemorrhage was noted often but in and of itself did not account for coronary thrombosis Such hemorrhages were found most often within the coronary tree of hearts which had a recent coronary thrombosis elsewhere in the vascular system This acute event may have led to abrupt flow changes in other portions of the coronary system associated changes in intraplaque pressures and resultant hemorrhage from damaged small vessels Such phenomena might lead to further endothelial attenuations and possibly future ulcerations

A point to be emphasized is the focal nature of intimal injury or endothelial disruption associated with coronary thrombosis Our studies and other similar studies point out the necessity for postmortem arteriograms and for some form of serial section histological technique when examining coronary arteries associated with thrombosis and myocardial infarction Areas of surface injury often were less than several hundred microns in length In the few cases in which we did not demonstrate intimal injury underlying thrombosis it is possible that sectioning coronary segments at smaller intervals might have revealed injuries Lack of detailed morphological studies employing coronary arteriography and serial sectioning of suspicious areas is a strong criticism against studies purporting to show a poor relationship between acute coronary lesions and myocardial infarction [2, 31]

Other criticisms have been enumerated in recent discussions[5] and a few are worthy of further comment In several studies subendocardial infarction has been noted to be infrequently associated with coronary thrombosis[5, 6, 7, 34] These lesions have been described as patchy or multicentric and usually not confined to the distribution of a single coronary artery[5] Rather than exclude such myocardial lesions we chose to

review them to avoid a prejudgment regarding their nature As described in the Results section, this type of myocardial lesion, which we prefer to designate as 'hypoperfusion necrosis' rather than myocardial infarct,' is associated with clinical events complicated by hypotension or transient coronary hypoperfusion This is not to say however, that all subendocardial lesions are unassociated with acute coronary lesions In this study a majority of subendocardial lesions were confined to the distribution of a single coronary artery and were associated with acute coronary lesions as described above

Inclusion of patients dying suddenly and unexpectedly while not under observation, patients with cardiac ischemia, and patients with arrhythmia related injury or death among studies of myocardial infarcts has also obscured the issue[31, 35, 36] It is *clear that such problems occur* with increased frequency in patients with coronary artery disease,[53, 55] but these abnormalities are not tantamount to myocardial infarction with associated coronary thrombosis Recognizable myocardial necrosis is a requisite for study of myocardial infarct coronary lesion relationships If one includes "ischemic deaths or sudden deaths without identifiable myocardial injury the relationships become unclear[3, 55]

Pertinent with regard to another problem is the group of myocardial lesions in this study caused by coronary embolization They constituted over 10 per cent of the cases and generally occurred in patients with minimal atherosclerotic coronary disease Although generally regarded as a rare event[5] myocardial infarction in the presence of normal coronary arteries has been described[57, 58] Since pathological information often cannot be obtained in such cases[59] embolization should be strongly considered in addition to other suggested etiologies of such phenomena including vaso spasm thrombosis with rapid lysis or possible metabolic derangements[38] Coronary emboli have been shown radiographically to resolve within weeks[60] and in the present study this is borne out histologically *with* previous partially or totally occlusive emboli becoming incorporated into coronary walls eventually becoming indistinguishable from atherosclerotic plaques[61]

In conclusion, this study has shown that an explanation for the overwhelming majority of myocardial lesions at least 3 cm in one dimension can be found in the coronary artery supplying that region Atherosclerotic related coronary lesions accounted for over 85 per cent of myocardial lesions and evidence from serial histological sections of coronary segments with acute lesions strongly suggests that endothelial and intimal damage in the form of plaque ulcerations erosions, or ruptures precipitates coronary thrombosis with resultant myocardial infarction These focal endothelial interface injuries are difficult to demonstrate and coronary arteriography and serial histological sections should be employed in the examination of the pertinent coronary segment Coronary artery thromboemboli accounted for over 10 per cent of the myocardial lesions Patchy, multicentric, subendocardial lesions not confined to the distribution of a single coronary artery were not associated with acute coronary lesions but with a clinical episode of hypotension and are better considered as hypo perfusion necrosis rather than a myocardial infarct

A complete understanding of the pathogenesis of most myocardial infarcts requires further knowledge of the factors producing atherosclerotic plaque ulceration It is clear that myocardial infarcts result from coronary artery occlusions and the majority of occlusions are thrombus deposits on ulcerated atheromata Since many thromboses show histological evidence of sequential accumulation and a greater age than the associated infarct, it seems reasonable to believe that appropriate anticoagulation therapy could prevent some myocardial infarcts

Summary

A review of 494 myocardial lesions at least 3 cm in one dimension revealed 418 (85 per cent) related to atherosclerotic coronary lesions, 55 (11 per cent) related to coronary emboli of various types, 18 (3 5 per cent) without specific coronary lesions but related to clinical events associated with coronary hypoperfusion, and 3 (0 5 per cent) associated with miscellaneous coronary lesions In 399 of 418 (96 per cent) atherosclerotic coronary lesions of all ages complete occlusion (remote or fresh) or histological evidence of lumenal recanalization was present These coronary lesions were situated within extramural coronary artery segments one to several centimeters proximal to the myocardial lesions which were confined to the distribution of the respective partially or totally occluded coronary segments

In the atherosclerotic coronary lesions less than 2 weeks of age partially or totally occlusive thrombus was found in 67 of 69 (97 per cent) cases and an underlying plaque ulceration erosion or rupture was present in 64 of 69 (93 per cent) instances These endothelial and intimal injuries were generally focal in nature often extending over a length of only 100 to 200 μ In no instance could it be stated with certainty that the oldest portion of the atherosclerotic ulceration thrombus complex was younger in age than its associated myocardial lesion On the contrary in 10 of 69 (14 per cent) of the cases portions of the coronary thrombus usually at the site of plaque ulceration were histologically older than the myocardial lesion In addition the presence of thrombus and plaque debris admixtures further suggested the antecedent nature of the coronary lesion in relation to the myocardial lesion

Atherosclerotic coronary lesions associated with myocardial lesions of 2 to 8 weeks of age had identifiable thromboses in all instances and underlying plaque ulcerations erosions or ruptures in 17 of 21 (80 per cent) Endothelial injuries were more difficult to assess due to the obscuring features of organizing lumenal thrombus Interface injuries i e plaque ulcerations erosions or ruptures were reliably detectable up to approximately one month of age

Coronary artery thromboemboli accounted for a significant percentage of myocardial lesions were usually associated with normal or minimal coronary artery disease and frequently involved smaller intramural coronary vessels of the heart Organization and recanalization of thromboemboli tended to be rapid and complete so that in the late stages the residual intimal plaque was sometimes difficult to identify

Myocardial lesions related to clinical events associated with coronary artery hypoperfusion were generally subendocardial patchy multicentric and not confined to the distribution of a single coronary artery They were unassociated with acute coronary lesions and histologically displayed contraction band necrosis more frequently than the embolic and atherosclerotic related lesions.

An explanation was found for the overwhelming majority of myocardial lesions Most significantly in atherosclerotic coronary thrombosis the underlying precipitating event and nidus for thrombus formation appeared to be focal endothelial injury usually manifest in the form of plaque ulceration erosion or disruption Interface injuries such as these were found underlying coronary thrombosis in 76 of 82 (93 per cent) arterial lesions associated with myocardial infarcts less than 1 month of age

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REFERENCES

1 Branwood, A. W and Montgomery G L Observations on the morbid anatomy of coronary artery disease Scot Med J 1 367 1956
2 Blumgart H L Schlesinger M J and Zoll P M Angina pectoris coronary failure and acute myocardial infarction J A M A 116 91 1941
3 Blumgart H L Schlesinger M J and Davis D Studies on the relation of the clinical manifestations of angina pectoris coronary thrombosis and myocardial infarction to the pathologic findings, Am Heart J 19 1 1940
4 Spain D M. and Bradess, V A The relationship of coronary thrombosis to coronary atherosclerosis and ischemic heart disease (a necropsy study covering a period of 25 years) Am J Med Sci. 240 701 1960
5 Friedberg C K and Horn H Acute myocardial infarction not due to coronary artery occlusion J A M A 112 1675 1939
6 Miller R D Burchell H B and Edwards J E Myocardial infarction with and without acute coronary occlusion Arch. Intern Med 88 597 1951
7 Meadows, R Coronary thrombosis and myocardial infarction Med J Aust 2 409 1965
8 Nathanson M H Disease of the coronary arteries Clinical and pathologic features, Am J Med Sci. 170 240 1925
9 Baroldi, G Acute coronary occlusion as a cause of myocardial infarct and sudden coronary heart death Am J Cardiol. 16 859 1965
10 Schwartz, C J and Mitchell J R A The relation between myocardial lesions and coronary artery disease I An unselected necropsy study Br Heart J 24 761 1962.
11 Mitchell J R. A and Schwartz, C J The relation between myocardial lesions and coronary artery disease II A selected group of patients with massive cardiac necrosis or scarring Br Heart J 25 1 1963
12. Duguid J B Thrombosis as a factor in the pathogenesis of coronary atherosclerosis J Pathol. Bacteriol. 58 207 1946
13 Kagan A Livsic A M., Sternby N., and Vihert A M Coronary artery thrombosis and the acute attack of coronary heart-disease Lancet 2 1199 1968
14 Harland, W A and Holburn A M Coronary thrombosis and myocardial infarction Lancet 2 1158 1968
15 Page D L Caulfield J B Kastor J A DeSanctis R W and Sanders C A. Myocardial changes associated with cardiogenic shock N Engl. J Med 285 133 1971
16 Herrick J B Thrombosis of the coronary arteries J A M A. 72 387 1919
17 Parkinson J and Bedford D E Cardiac infarction and coronary thrombosis Lancet 1 4 1928

18 Morgan A D The pathogenesis of coronary occlusion Oxford 1957 Blackwell Scientific Publications
19 Davis N A Incidence of thrombosis in myocardial infarction Aust N Z J Med **19** (Suppl) 60 1970
20 Hackel D B Estes E H Walston A Kott S and Day E Some problems concerning coronary artery occlusion and acute myocardial infarction Circulation **39-40** (Suppl IV) 31 1969
21 Constantinides P Plaque fissures in human coronary thrombosis Atherosclerosis **6** 1 1966
22 Friedman M and Van den Bovenkamp G J The pathogenesis of a coronary thrombus Am J Pathol **48** 19 1966
23 Chapman I Morphogenesis of occluding coronary artery thrombosis Arch Pathol **80** 256 1965
24 Friedman M The coronary thrombus Its origin and fate Hum Pathol **2** 81 1971
25 Jorgensen L Chandler A B and Borchgrevink C F Acute lesions of coronary arteries in anticoagulant treated and in untreated patients Atherosclerosis **13** 21 1971
26 Bouch D C and Montgomery G L Cardiac lesions in fatal cases of recent myocardial ischaemia from a coronary care unit Br Heart J **32** 795 1970
27 Chapman I Relationships of recent coronary artery occlusion and acute myocardial infarction J Mt Sinai Hosp **35** 149 1968
28 Chapman I The initiating cause of coronary artery thrombosis an anatomic study J Mt Sinai Hosp **36** 361 1969
29 Sinapius D Beziehungen zwischen Koronarthrombosen and Myokardinfarkten Dtsch Med Wochenschr **97** 443 1972
30 Sinapius D Zur morphologie verschliessender Koronar thromben Dtsch Med Wochenschr **97** 544 1972
31 Roberts W C and Buja L M The frequency and significance of coronary arterial thrombi and other obser vations in fatal acute myocardial infarction A study of 107 necropsy patients Am J Med **52** 425 1972
32 Erhardt L R Lundman T and Mellstedt H Incor poration of I labelled fibrinogen into coronary arterial thrombi in acute myocardial infarction in man Lancet **1** 387 1973
33 Walston A Hackel D B and Estes E H Acute coronary occlusion and the power failure syndrome AM HEART J **79** 613 1970
34 Erhlich J C and Shinohara Y Low incidence of coronary thrombosis in myocardial infarction A restudy by serial block technique Arch Pathol **78** 432 1964
35 Chapman I The cause effect relationship between recent coronary artery occlusion and acute myocardial infarction AM HEART J **87** 267 1974
36 Roberts W C Coronary thrombosis and fatal myocar dial ischemia Circulation **49** 1 1974
37 Robbins S L Cardiac pathology—a look at the last five years Part 1 Hum Pathol **5** 9 1974
38 MacAlpin R N Fugitive coronary occlusion N Engl J Med **291** 470 1974
39 Chandler A B Chapman I Erhardt L R Roberts W C Schwartz C J Sinapius D Spain D M Sherry S Ness P M and Simon T L Coronary thrombosis in myocardial infarction Am J Cardiol **34** 823 1974
40 Hutchins G M and Anaya O A Measurements of cardiac size chamber volumes and valve orifices at autopsy Johns Hopkins Med J **133** 96 1973
41 Fetting J H Griffith L S C Brawley R K and Hutchins G M Myocardial lesions in patients operated upon under cardiopulmonary bypass In preparation
42 Bouchardy B and Majno G Histopathology of early myocardial infarcts Am J Pathol **74** 301 19 4
43 Jennings R B Sommers H M Herdsen P B and Kaltenbach J P Ischemic injury of myocardium, Ann. N Y Acad Sci **156** 61 1969
44 Reichenbach D C and Benditt E P Myofibrillar degeneration a response of the myocardial cell to injury Arch Pathol **85** 189 1968
45 Bulkley B H Ridolfi R L Salyer W R and Hutchins, G M Myocardial lesions of progressive systemic sclerosis A cause of cardiac dysfunction Circu lation In press March 19/6
46 Hutchins G M and Bannayan G A Development of endocardial fibroelastosis following myocardial infarc tion Arch Pathol **91** 113 1971
47 Salyer W R Page D L and Hutchins, G M The development of cardiac myxomas and papillary endocar dial lesions from mural thrombus, AM HEART J 89 4 1975
48 Friesinger G C Page E E and Ross R S Prognostic significance of coronary arteriography Trans Assoc Am Physicians **83** 78 1970
49 Mitchell J R A and Schwartz C J Arterial disease Philadelphia 1965 F A Davis Company pp 109 113
50 Saphir O Priest W S Hamburger W H and Katz L N Coronary arteriosclerosis coronary thrombosis and the resulting myocardial changes AM HEART J **10** 762 1935
51 Clark E Graef I and Chasis H Thrombosis of the aorta and coronary arteries With special reference to the fibrinoid lesions Arch Pathol **22** 183 1936
52 Feil H Preliminary pain in coronary thrombosis Am J Med Sci **193** 42 1937
53 Thomas W A Underlying causes of myocardial ischemia (atherosclerotic and nonathero clerotic) in Edwards, J E Lev M and Abell M R editors The heart Baltimore 1974 The Williams & Wilkins Company
54 Ryan M Lown B and Horn H Comparison of ventricular ectopic activity during 24 hour monitoring and exercise testing in patients with coronary heart disease N Engl J Med **292** 224 1975
55 Spain D M The pathogenesis of sudden cardiac death and the sequelae of myocardial infarction in Edwards, J E Lev M and Abell M R editors The heart Baltimore 1974 The Williams & Wilkins Company
56 Proudfit W L Shirey E K and Sones F M Jr Selective cine coronary arteriography Correlation with clinical findings in 1 000 patients Circulation **33** 901 1966
57 Likoff W Myocardial infarction in subjects with normal coronary arteriograms Am J Cardiol **28** 742 1971
58 Kimbiris D Segal B L Munir M et al Myocardial infarction in patients with normal patent coronary arteries as visualized by cinearteriography Am J Cardiol **29** 724 1972
59 Khan A H and Haywood L J Myocardial infarction in nine patients with radiologically patent coronary arteries N Engl J Med **291** 427 1974
60 O Reilly R J and Spellberg R D Rapid resolution of coronary arterial emboli Ann Intern Med **81** 348 1974
61 Salyer W R Salyer D C and Hutchins, G M Local arterial wall injury caused by thromboemboli Am J Pathol **75** 285 1974

The effect of ouabain on nutritional circulation and regional myocardial blood flow

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The use of digitalis in the treatment of angina pectoris or myocardial infarction has been of variable clinical benefit [1,2] The different responses seen after administration of digitalis may be partially explained by differences in the inotropic state of the heart In the nonfailing myocardium with coronary artery disease digitalis may increase myocardial oxygen consumption (MVO) aggravate the imbalance between oxygen supply and demand and produce angina pectoris However in the dilated failing ventricle digitalis may decrease heart size and wall tension thus reducing MVO_2 and relieving myocardial hypoxia

The effects of digitalis on the distribution of blood flow between epicardium and endocardium of the left ventricle may also be expected to differ in the failing and nonfailing myocardium Nelson and co workers have shown that ouabain or acetylstrophanthidin increased endocardial blood flow in an ischemic failing heart Experiments in the nonfailing heart with constant total coronary blood flow have not been performed

In the present study a comparison was made of the effect of ouabain on total effective capillary blood flow as measured by the rubidium 86 extraction technique and the distribution of total coronary blood flow as determined by the radioactive microsphere method [7] The results suggest that ouabain increases MVO_2 and reduces effective capillary blood flow by producing a shunting of blood away from the endocardium of the left ventricle under conditions of a constant coronary blood flow in the nonfailing heart The increases in left ventricular systolic pressure produced by ouabain may be responsible for the shift in blood flow

Methods

Isolated supported heart preparation (ISHP) Mongrel dogs of either sex weighing between 13 and 20 kilograms were fasted overnight anesthetized with pentobarbital sodium (30 mg per kilogram intravenously) and ventilated by a respirator (Harvard Model 607) with room air at 10 to 15 breaths per minute Atelectasis was prevented by maintaining an expiratory pressure of 5 to 7 cm H O with a trap Arterial blood pH was maintained between 7 35 and 7 45 by intravenous infusion of 1 5 per cent sodium bicarbonate when necessary After midsternal thoracotomy the heart was suspended in a pericardial cradle Surgical procedure for isolation and perfusion of the recipient heart has been described Briefly the heart was isolated *in situ* and the coronary arteries perfused with heparinized (5 0 mg per kilogram) arterial blood at 37° C from a donor dog via retrograde flow through the brachiocephalic artery Total coronary blood flow was adjusted by means of a roller pump (Sarns Model 3500) to provide a perfusion pressure of 90 mm Hg Coronary venous drainage into the right atrium and ventricle was returned to a femoral

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vein of the donor dog by means of a large bore cannula inserted into the right ventricle A small multihole catheter was placed in the left ventricle to drain Thebesian and aortic regurgitant flow A flow transducer was inserted into the arterial inflow tubing and total coronary blood flow measured by use of a 270 Hz square wave electromagnetic flowmeter (Carolina Medical Instruments 322) Coronary blood flow in milliliters per minute per 100 Gm was calculated from *in situ* calibration curves (milliliters per minute) and heart weight (grams) Coronary artery perfusion pressure was measured by a catheter inserted into the arterial flow cannula and a strain gauge pressure transducer (Statham P 23 AC)

A thin latex balloon was placed in the left ventricle through the mitral valve and inflated with saline (5 to 15 ml) to provide an initial left ventricular systolic pressure of 100 mm Hg The balloon was tied securely at the mitral valve to prevent the possibility of slippage into the atrium Maximal dp/dt was obtained by electronic differentiation of the left ventricular pressure pulse A Brodie Walton strain gauge arch was sutured to the left ventricular wall perpendicular to the left anterior descending coronary artery to determine isometric contractile force Initially the strain gauge arch was stretched 50 per cent greater than resting tension and changes in contractile force were expressed as per cent of control The electrocardiogram (ECG) (limb Lead II) was also monitored Heart rate was maintained constant in the microsphere experiments by left ventricular pacing with a stimulator (Grass Model S18) The ECG left ventricular systolic pressure dp/dt coronary blood flow coronary artery perfusion pressure contractile force and donor blood pressure were continuously recorded on a polygraph (Grass Model 7)

Blood pH Po and Pco were measured at 37° C with an Instrumentation Laboratories Model 313 blood gas analyzer Before and during experimental interventions simultaneous arterial and coronary venous blood samples were withdrawn in glass syringes rinsed with 2 per cent NaEDTA Samples were stored on ice and subsequently used for measurement of blood pH Po Pco and oxygen content

Myocardial oxygen consumption Direct measurement of arterial and coronary venous blood oxygen content was made with duplicate 20 μl samples by an electrolytic cell method (Lex O Con Lexington Instrument Co) Myocardial oxygen consumption was calculated from the following equation

$$MVO = \frac{(AO - VO) \times CBF}{\text{heart weight (Gm)}} \times 100$$

where MVO_2 = total myocardial oxygen consumption expressed as milliliters of O utilized per minute per 100 Gm of heart weight, AO_2 and VO = arterial and venous oxygen content in volumes per cent (milliliters per 100 ml) CBF = total coronary blood flow (milliliters per minute) Per cent extraction of oxygen by the myocardium was calculated from the A V oxygen content difference divided by the arterial oxygen content

Rubidium 86 extraction technique The procedure for determination of rubidium 86 extraction (E Rb) and the calculated values for Rb clearance (C Rb) and the capillary transport coefficient (PS) has been described[6] A constant portion (6 to 8 ml per minute) of coronary venous blood flow was diverted through a well type gamma counter (Nuclear Chicago DS 202) and the total radioactivity calculated after correction for efficiency of the gamma counter at the given flow rate Per cent extraction of Rb during a single passage through the myocardium was calculated from the difference between the amount injected on the arterial side and the amount recovered on the venous side divided by the amount injected

$$E\ Rb = \frac{\text{Rb injected} - \text{Rb recovered}}{\text{Rb injected}}$$

The clearance (milliliters per minute per 100 Gm) of Rb by the heart was calculated as follows

$$C\ Rb = \frac{E\ Rb \times CBF}{\text{heart weight (Gm)}} \times 100$$

A formula relating CBF E Rb permeability factor (P) and total capillary membrane surface (S) has been derived by Renkin and expressed as the capillary transport coefficient (PS) The PS values (milliliters per minute per 100 Gm) were calculated as follows

$$PS = CBF \times \ln (1 - E\ Rb)$$

where CBF = total coronary blood flow in milliliters per minute per 100 Gm of heart weight ln = base of the natural logarithm E Rb = extraction of Rb during a single passage through the heart

Regional myocardial blood flow The distribution of coronary blood flow was determined by

use of the radioactive *microsphere technique*.[9] Carbonized plastic microspheres used in this study were labeled with [141]Ce (specific activity 8 1 mCi per gram) [51]Cr (specific activity 30 4 mCi per gram) [85]Sr (specific activity 10 7 mCi per gram) or [46]Sc (specific activity 11 7 mCi per gram) and were 16 0 ± 2 0 16 2 ± 2 3 15 9 ± 2 0 and 14 9 ± 1 5 μ in diameter respectively Microspheres were obtained as 1 mCi of nuclide in 5 ml of saline to which 1 drop of Tween 80 was added to minimize aggregation After appropriate dilution the mixture was agitated immediately prior to injection in a vortex mixer (Cole Parmer Model 4722) for 10 minutes Microspheres (2 to 3 μCi 75 000 to 150 000 spheres) were injected in a random order into the arterial inflow line in a total volume of 0 2 to 0 5 ml 30 cm from the *cannulated brachiocephalic artery* The total number of microspheres of each type injected was selected to provide a final sphere density of at least 400 spheres per tissue sample No significant change in coronary hemodynamics was seen *during or immediately* following microsphere injection

After completion of the experiment the recipient heart was excised washed with saline blotted dry and weighed The heart was fixed in formalin for 48 hours After rinsing in water epicardial fat large vessels atrial cap valves papillary muscle and chorda tendinae were removed and the ventricles sectioned into tissue areas Both ventricles were divided into anterior and *posterior* halves and subdivided *into base* middle (left ventricle only) and apex Each of the 10 tissue areas was further divided into epicardial and endocardial layers of approximately equal size The 20 tissue samples were weighed placed in glass scintillation vials and the activity of each isotope determined in duplicate at four energy windows in a Nuclear Chicago 1195 autogamma spectrometer equipped with dual channel analyzer Samples were approximately the same size (2 Gm) to reduce the variation of *internal ab orp* tion of gamma radiation True activity of each isotope was separated by a preprogrammed *computer* (Monroe Model 1860)

Three experimental groups were completed

Group 1 (rubidium 86 extraction N = 6) In the first series the effect of an intravenous dose of ouabain (25 μg per kilogram) on the extraction of [86]Rb was *examined* Initially the ISHP was allowed to stabilize at a coronary blood flow sufficient to produce a coronary *artery perfusion* pressure of 90 mm Hg and thereafter flow was maintained constant After two control determinations ouabain was administered and E Rb determined at the peak inotropic effect (approximately 20 minutes)

Group 2 (increasing left ventricular systolic pressure N = 6) In the second group of exper

Table I Effect of ouabain on myocardial hemodynamics and oxygen consumption in the ISHP (N = 6)

Parameter	*Before and at the peak effect of ouabain (25 μg/Kg intravenously)* Control (X ± S E)	Ouabain (X ± S E)
A oxygen content (vol %)	21 3 ± 0 2	21 1 ± 0 4
V oxygen content (vol %)	15 6 ± 0 7	14.3 ± 1 2
A V oxygen content (vol. %)	5 7 ± 0 7	6 7 ± 1 1
Oxygen extraction (%) [(AO – VO)/AO]	26.5 ± .6	31 8 ± 2 9
Myocardial oxygen consumption (mL/min /100 Gm.)	3 6 ± 0 4	4 2 ± 0 5†
Heart rate (beats/min)	114 0 ± 4 8	117 0 ± 4.8
Contractile force (%)	100	172 1 ± 3 6‡
Coronary artery perfusion pressure (mm Hg)	89 0 ± 5 5	85 0 ± 7 2
Left ventricular systolic pressure (mm Hg)	97 7 ± 2 8	114 2 ± 5 3†
Coronary blood flow (mL/min / 100 Gm.)	67 1 ± 5 4	6_ 1 ± 5 4

*Significantly different from control at P < 0 05 by a paired comparison.

†Significantly different from control at P < 0 01 by a paired comparison

‡Significantly different from control at P < 0 001 by a paired comparison

Table II Effect of ouabain on extraction of rubidium 86 (E Rb) rubidium 86 clearance (C Rb) and capillary transport coefficient (PS) in the ISHP (N = 6)

Parameter	*Before and at the peak effect of ouabain (25 μg/Kg intravenously)* Control (X ± S E)	Ouabain (X ± S.E)
E[86]Rb (%)	73 7 ± 1 6	69 9 ± 2 0
C[86]Rb (ml /min /100 Gm)	45 3 ± 3 2	42 ? ± 2 6
PS[86]Rb (ml /min /100 Gm)	81 8 ± 4 1	71 4 ± 2 8

Significantly different from control at P < 0 01 by a paired comparison

Table III Effect of ouabain on myocardial hemodynamics and oxygen consumption in the ISHP where left ventricular systolic pressure was allowed to increase (N = 6)

Parameter	Before and during ouabain infusion (10 µg/min intracoronary)		
	Control ($\bar{X}$ ± S.E.)	Ouabain (50 ± 7.7 µg)* ($\bar{X}$ ± S.E.)	Ouabain (99.2 ± 8.4 µg)* ($\bar{X}$ ± S.E.)
A oxygen content (vol %)	21.8 ± 0.6	21.9 ± 0.6	22.2 ± 0.6
V oxygen content (vol %)	17.1 ± 0.5	15.4 ± 0.7†	14.[illegible] ± 0.6†§
A-V oxygen content (vol %)	4.7 ± 0.1	6.5 ± 0.2‡	8.0 ± 0.3‡§
Oxygen extraction (%) [(AO₂ − VO₂)/AO₂]	21.6 ± 0.7	29.9 ± 1.4†	36.[illegible] ± 1.4‡§
Myocardial oxygen consumption (ml./min./100 Gm.)	4.9 ± 0.6	6.8 ± 0.9†	8.4 ± 1.[illegible]§
Heart rate (beats/min.)	150	150	150
Contractile force (%)	100	125‡	150‡§
Coronary artery perfusion pressure (mm. Hg)	91.0 ± 2.4	100.2 ± 4.7†	98.[illegible] ± 8.0
Left ventricular systolic pressure (mm. Hg)	100	141.7 ± 3.8‡	[illegible] ± [illegible]5‡§
dp/dt (mm. Hg/sec.)	1154 ± 103	1363 ± 103‡	[illegible] ± [illegible]4‡§
Coronary blood flow (ml./min./100 Gm.)	105.0 ± 14.4	105.0 ± 14.4	105.0 ± 14.4

*Total cumulative dose.
†Significantly different from control at P < 0.01 by a paired comparison.
‡Significantly different from control at P < 0.001 by a paired comparison.
§Significantly different from preceding ouabain value at P < 0.05 by a paired comparison.

iments ouabain (10 µg per minute) was administered as an intracoronary infusion. Microspheres were injected during the control period and when myocardial contractile force was 25, 50, and 100 per cent above control. Heart rate was controlled at 150 beats per minute by left ventricular pacing. Coronary blood flow was maintained constant.

Group 3 (constant left ventricular systolic pressure, N = 8). In the final group of experiments ouabain (10 µg per minute) was again given as an intracoronary infusion. Microspheres were injected during the control period and when myocardial contractile force was 25, 50, and 100 per cent above control. Left ventricular systolic pressure and heart rate were controlled at 100 mm. Hg and 150 beats per minute by adjusting left ventricular balloon volume and left ventricular pacing, respectively. Coronary blood flow was maintained constant.

Data analysis. Transmural distribution of coronary blood flow was expressed as the ratio of counts per gram epicardium to counts per gram endocardium (epi/endo). Statistical analysis of results was made by use of Student's t test for paired samples.[11] The difference between epicardial/endocardial ratios and hemodynamic or blood gas data were considered significant when P < 0.05.

Results

Effect of ouabain on rubidium 86 extraction. The results presented in Table I summarize the effects of ouabain (25 µg per kilogram intravenously) on myocardial hemodynamics and oxygen consumption (MVO_2) in six ISHP. Ouabain produced a decrease in coronary venous oxygen content and a significant increase in A-V oxygen difference, oxygen extraction, and MVO_2. The increase in MVO_2 was paralleled by a significant increase in contractile force and left ventricular systolic pressure. Heart rate and coronary artery perfusion pressure did not change. Ouabain significantly decreased E Rb, C Rb, and PS by the myocardium (Table II).

Effect of ouabain on regional myocardial blood flow: increasing left ventricular systolic pressure. The results presented in *Table III* summarize the effects of an intracoronary infusion of ouabain (10 µg per minute) on myocardial hemodynamics and MVO_2 in six ISHP. Ouabain (total doses = 50 ± 7.7 and 99.2 ± 8.4 µg) produced a significant decrease in coronary venous oxygen content and a significant increase in A-V oxygen difference, oxygen extraction, and MVO_2. The increase in MVO_2 was paralleled by a significant increase in contractile force, left ventricular systolic pressure, and *dp/dt*. Coronary artery perfusion pressure was significantly increased at the lower cumulative dose of ouabain.

The results in Figs. 1 and 2 show the effect of ouabain infusion on the epi/endo of the whole left ventricle during a 25, 50, and 100 per cent increase in contractile force. Only three experiments were completed in which a 100 per cent increase in

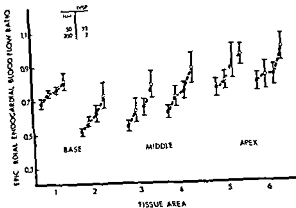


Fig 1 Effect of increasing myocardial contractile force (per cent of control) and left ventricular systolic pressure (mm Hg) by intracoronary infusion of ouabain (10 μg per minute) on the transmural distribution of coronary blood flow in six tissue areas of the left ventricle Tissue areas *1* and *2* represent the anterior and posterior base *3* and *4* the anterior and posterior middle *5* and *6* the anterior and posterior apex Each of the first three points represents the mean ± S E M (N = 6) The final point represents the mean ± S E M (N = 3)

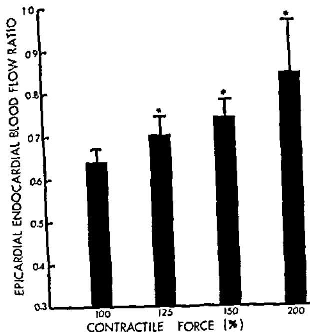


Fig 2 Effect of increasing myocardial contractile force (per cent of control) and left ventricular systolic pressure (mm Hg) by intracoronary infusion of ouabain (10 μg per minute) on the transmural distribution of coronary blood flow in the whole left ventricle Each of the first three bars represent the mean ± S E M (N = 6) The final bar represents the mean ± S E M (N = 3) P values were calculated by a paired comparison (P < 0 05)

contractile force was achieved because of the development of severe ventricular arrhythmias and fibrillation due to ouabain toxicity As contractile force and left ventricular systolic pressure were increased by ouabain blood flow was significantly shifted away from the endocardium of the left ventricle (Fig 2) Increases in epi/endo occurred in all tissue areas (Fig 1) No significant change was observed in the epi/endo of the right ventricle

Effect of ouabain on regional myocardial blood flow constant left ventricular systolic pressure The results presented in Table IV summarize the effects of an intracoronary infusion of ouabain (10 μg per minute) on myocardial hemodynamics and MVO in eight ISHP Left ventricular systolic pressure and heart rate were controlled at 100 mm Hg and 150 beats per minute by adjusting left ventricular balloon volume and by cardiac pacing Ouabain (total doses = 38 3 ± 6 2 68 1 ± 8 8 and 128 8 ± 8 0 μg) produced a significant decrease in coronary venous oxygen content and a significant increase in A V oxygen difference oxygen extraction and MVO The increase in MVO was paralleled by a significant increase in contractile force dp/dt and coronary artery perfusion pressure

The results depicted in Figs 3 and 4 show the effect of ouabain infusion on the epi/endo in the different tissue areas of the left ventricle and the mean epi/endo of the left ventricle during a 25 50 and 100 per cent increase in contractile force No significant change in epi/endo of any tissue area of the left ventricle was observed during drug infusion (Fig 3) Similarly no change in epi/endo was seen in the right ventricle

Discussion

Radioactive tracers have been used to measure various aspects of regional myocardial blood flow This includes the total coronary blood flow or nutritional circulation Diffusible tracers such as rubidium 86 have been used for determining that portion of the total coronary blood flow which perfuses the capillary bed (nutritional blood flow) based on the extraction or clearance principle [3, 4] Previous work from this laboratory has shown that sympathomimetic amines[6] produce an increase in heart rate left ventricular systolic pressure myocardial contractility and myocardial oxygen consumption and a decrease in E Rb C^{86}Rb and PS [11] It was proposed that the decrease in effective capillary blood flow and increase in myocardial oxygen consumption may be important factors in producing an imbalance

Table IV Effect of ouabain on myocardial hemodynamics and oxygen consumption in the ISHP where left ventricular systolic pressure was maintained constant (N = 8)

Parameter	*Before and during ouabain infusion (10 μg/min intracoronary)*			
		Ouabain		
	Control (X ± S E)	*(38 3 ± 6 2 μg) (X ± S E)*	*(68 1 ± 8 8 μg)* (X ± S E)*	*(128 8 ± 8 0 μg) (X ± S E)*
A oxygen content (vol %)	21 4 ± 1 0	21 2 ± 1 1	21 1 ± 1 1	21 4 ± 1 0
V oxygen content (vol %)	14 9 ± 1 1	13 7 ± 0 8 ‡	12 9 ± 0 8 ‡	11 7 ± 0 8 ‡
A V oxygen content (vol %)	6 4 ± 1 0	7 6 ± 0 8†§	8 3 ± 0 9†§	9 7 ± 0 9†§
Oxygen extraction (%) [(AO − VO)/AO,]	30 1 ± 4 2	35 4 ± 3 1†§	38 9 ± 3 5* ‡	45 3 ± 3 5†‡
Myocardial oxygen consumption (ml /min /100 Gm)	4 7 ± 0 4	5 7 ± 0 4	6 1 ± 0 4	7 4 ± 0 6
Heart rate (beats/min)	150	150	150	150
Contractile force (%)	100	125	150	200
Coronary artery perfusion pressure (mm Hg)	94 8 ± 2 4	100 8 ± 2 6 *‡	100 5 ± 3 7 *	95 4 ± 3 2
Left ventricular systolic pressure (mm Hg)	100	100	100	100
dp/dt (mm Hg/sec)	1231 ± 101	1332 ± 96†§	1402 ± 90†§	1531 ± 90†§
Coronary blood flow (ml /min /100 Gm)	84 4 ± 11 5	84 4 ± 11 5	84 4 ± 11 5	84 4 ± 11 5

Total cumulative dose
Significantly different from control at P < 0 05 by a paired comparison
†Significantly different from control at P < 0 01 by a paired comparison
‡Significantly different from preceding value at P < 0 05 by a paired comparison
§Significantly different from preceding value at P < 0 01 by a paired comparison

in the ratio of oxygen supply to oxygen demand in patients with coronary artery disease during stress or exercise

Normally it is thought that capillary membrane permeability to diffusion of Rb is not limiting at physiological levels of coronary blood flow[14] Thus the decrease in the extraction of Rb was assumed to be due to a decrease in effective capillary flow and surface area for diffusion Two mechanisms were proposed to help explain the effect of catecholamines on effective capillary blood flow Either anatomical arterial venous (A V) shunts were opened so that the ratio of blood flowing through capillaries versus A V shunts was changed in favor of the latter or the distribution of blood flow between epicardium and endocardium was changed in favor of epicardium Recent work[1] has shown that the endocardium extracts more oxygen than the epicardium which suggests that the epicardium may be over perfused and act as a physiological shunt A shift in the ratio of flow between these two regions could explain the decrease in extraction of Rb seen during catecholamine or ouabain administration in the ISHP Warltier and co workers[1] have shown that an intracoronary infusion of norepinephrine increases epi/endo in the ISHP perfused at constant coronary blood flow These results[18] and the present ones with ouabain support the hypothesis of a regional change in blood flow distribution No radioactivity (15 μ microspheres) was found in the coronary venous blood before or during ouabain infusion However, this does not rule out the possibility that A V shunts less than 15 μ in diameter exist in the myocardium More likely, ouabain produces a functional shunting of blood flow away from the endocardium to epicardium

Ouabain infusion produced a shift in blood flow away from the endocardium only when increases in contractile state of the myocardium were accompanied by increases in left ventricular systolic pressure Apparently as left ventricular pressure increases a mechanical obstruction to flow occurs in the endocardium during systole These results relate to the observations of Snyder Downey, and Kirk[1] who have studied the relative contribution of ventricular pressure

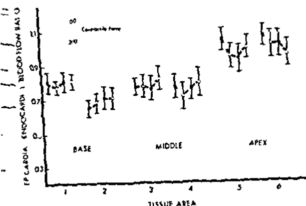


Fig 3 Effect of increasing myocardial contractile force (per cent of control) by intracoronary infusion of ouabain (10 μg per minute) on the transmural distribution of coronary blood flow in six tissue areas of the left ventricle Left ventricular systolic pressure was maintained constant at 100 mm Hg Each point represents the mean ± S E M (N = 8)

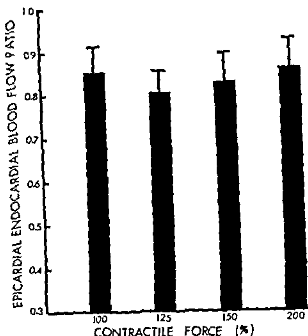


Fig 4 Effect of increasing myocardial contractile force (per cent of control) by intracoronary infusion of ouabain (10 μg per minute) on the transmural distribution of coronary blood flow in the whole left ventricle Left ventricular systolic pressure was maintained constant at 100 mm Hg Each bar represents the mean ± S E M (N = 8) No significant changes were observed

and myocardial contractility to extravascular resistance These authors concluded that 75 per cent of extravascular resistance is due to passive stresses which are in equilibrium with ventricular pressure and that large increases in myocardial contractility *per se* have a small effect on the amount of compression experienced by the coronary arteries Thus in the present study it is likely that an increased impedance to coronary flow occurs in the endocardium due to increased extravascular or myocardial tissue pressure as a result of the increase in left ventricular systolic pressure In support of this concept recent experiments from our laboratory have shown that a mechanical increase in left ventricular systolic pressure (0 to 225 mm Hg) resulted in an increase in the epi/endo (0 72 to 0 83) of the left ventricle (unpublished observations) Furthermore these results are in agreement with those of L Abbate and co workers who stressed the importance of the ratio of coronary artery perfusion pressure to left ventricular systolic pressure in determining regional blood flow distribution in isolated hearts These authors found an increase in epi/endo as the ratio (CAPP/LVSP) decreased Similar results were observed in the present study

Previous work has shown that digitalis glycosides produce a vasoconstrictor effect in a number of organs as well as the heart However controversy exists as to whether the vasoconstriction seen in the coronary bed is neurally mediated via alpha adrenergic receptor stimulation or due to a direct action of digitalis on the coronary vessels In the present study an intracoronary infusion of ouabain produced an increase in coronary vascular resistance (increased coronary artery perfusion pressure at a constant coronary blood flow) whether left ventricular systolic pressure was maintained constant or not These results indicate that the increase in coronary vascular resistance was not simply due to an increase in intramyocardial tissue pressure The augmentation of coronary vascular resistance during increased myocardial oxygen consumption which would tend to dilate the coronary vascular bed indicates that the direct constrictor action of ouabain was actually underestimated In contrast similar increases in myocardial oxygen consumption produced by intracoronary infusion of norepinephrine resulted in a fall in coronary vascular resistance It is concluded that ouabain has a direct coronary vasoconstrictor action in the ISHP However these findings do not rule out the possibility of an additional neurally mediated vasoconstrictor effect of the digitalis glycosides in the intact heart

The results of the present study and others[1-3] indicate that the digitalis glycosides should not be used indiscriminately in patients with angina pectoris or recent myocardial infarction when heart failure is not evident In patients with coronary heart disease where the coronary blood flow reserve is limited or absent, the administration of digitalis may exacerbate the imbalance between oxygen supply and demand to the myocardium by three potential mechanisms an increase in myocardial oxygen consumption, a reduction in total coronary blood flow by a direct vasoconstrictor action, and a decrease in endocardial perfusion It is likely that these effects were observed in the present study in the canine heart where the coronary vasculature was probably normal and heart failure was absent In addition the arrhythmia producing potential of these compounds is well known especially in the presence of myocardial ischemia On the other hand, the digitalis glycosides may produce beneficial effects in the patient with angina pectoris or recent myocardial infarction with a failing ventricle Nelson Sonnenblick and Kirk[4] have shown that digitalis administration results in a decrease in myocardial oxygen consumption via a decrease in heart size in the ischemic failing canine heart and increases endocardial perfusion by a reduction of systolic and diastolic extravascular compression A recent clinical study has shown the effectiveness of combining propranolol and digoxin in patients with angina pectoris who have abnormal ventricular function or enlarged hearts In addition the use of ouabain has been shown to produce an improvement in various indices of ventricular function in patients with an acute myocardial infarction accompanied by an elevated left ventricular end diastolic pressure Thus it can be concluded that digitalis may be beneficial in anginal patients or following acute myocardial infarction if cardiac failure is present In this select group digitalis may improve myocardial oxygen supply demand relationships However the effect of digitalis on the epicardial/endocardial blood flow ratios may be limited or potentiated by the extent and distribution of lesions in the large epicardial vessels

Summary

The effect of ouabain on myocardial nutritional circulation (rubidium 86 extraction) and regional myocardial blood flow (radioactive microspheres) was studied in the isolated supported canine heart preparation perfused at a constant coronary blood flow Ouabain (25 μg per kilogram, intravenously) produced a significant increase in myocardial contractile force peak left ventricular systolic pressure and myocardial oxygen consumption Ouabain also decreased rubidium 86 extraction (E Rb) rubidium 86 clearance (C Rb) and the capillary transport coefficient (PS) Intracoronary infusion of ouabain (10 μg per minute) produced significant increases in contractile force (25 50 and 100 per cent above control), left ventricular systolic pressure myocardial oxygen consumption and the epicardial endocardial blood flow ratio (epi/endo) of the left ventricle When left ventricular systolic pressure was held constant (100 mm Hg) ouabain infusion (10 μg per minute intracoronary) increased myocardial contractile force (25 50, and 100 per cent above control) and myocardial oxygen consumption but did not change the epi/endo of the left ventricle These results suggest that ouabain reduces E Rb C Rb and PS by producing a shunting of blood flow from endocardium to epicardium in the left ventricle The increase in left ventricular systolic pressure appears to be responsible for these change

The authors wish to acknowledge the skillful technical assistance of Wayne Herrick and Mark Diemer

REFERENCES

1 Harding P R Aronow W S and Eisenman J Digitalis as an antianginal agent Chest 64 439 1973
2 Morrison J Pizzarello R Reduto L and Gulotta S Effect of digitalis on predicted myocardial infarction size in man Clin Res 23 198 1975
3 Crawford M H LeWinter M M O Rourke R A Karliner J S and Ross J Combined propranolol and digoxin therapy in angina pectoris Ann Intern Med 83 449 1975
4 Nelson G R Sonnenblick E H and Kirk E S Mechanism of the salutory effects of digitalis on myocardial ischemia with failure Clin Res 23 387 1975
5 Winbury M M Role of myocardial nutritional circulation in evaluation of antianginal agent in Winbury M M editor Problems in laboratory evaluation of antianginal agents Amsterdam 1967 North Holland Publishing Company p 26
6 Somani P Laddu A R and Hardman H F Nutritional circulation in the heart III Effect of isoproterenol and beta adrenergic blockade on myocardial hemodynamic and rubidium 86 extraction in the isolated supported heart preparation J Pharmacol Exp Ther 175 577 1970
7 Rudolph A M and Heymann M A The circulation of the fetus in utero Methods for studying distribution of blood flow cardiac output and organ blood flow Circ Res 21 163 1967
8 Renkin E M Transport of potassium 42 from blood to

tis ue in isolated mammalian keletal muscles Am J Phy iol 197 1705 1959
9 Domenech R J Hoffman J I E Noble M I M Saunders K B Hen on J R and Subijanto S Total and regional coronary blood flow mea ured by radioac tive micro pheres in conscious and anesthetized dogs Circ Res 25 581 1969
10 Buckberg G D Luck J D Payne D B Hoffman J I E Archie J P and Fixler D E Some ources of error in measuring regional blood flow with radioactive micro pheres J Appl Physiol 31 598 1971
11 Snedecor G W and Cochran W G Stati tical meth od ed 6 Ames Iowa 196 Iowa State University Pres
12 Hymar C Powell S Rosen A Sonnen chein R R and Lyna B Effect of alteration of total muscular blood flow and local ti sue clearance of radioiodide in the cat Acta Phy iol Scand 46 358 1959
13 Somani P Laddu A R and Hardman H F Nutri tional circulation in the heart I Effect of changes in heart rate on myocardial oxygen con umption and nutri tional circulation with con tant coronary blood flow Life Sci 8 1151 1969
14 Renkin E M Blood flow and transcapillary exchange in skeletal muscle Fed Proc 24 1092 1965
15 Gamble W J LaFarge C G Fyler D C Weisul J and Monroe R G Regional coronary venou oxygen saturation and myocardial oxygen ten ion following abrupt changes in ventricular pres ure in the isolated dog heart Circ Res 34 672 1974
16 Warltier D C Hardman H F, Laddu A R Somani P and Gros G J Myocardial di tribution of coronary blood flow in the isolated upported heart preparation Cardio asc Res 9 634 1975
17 Snyder R Downey J M and Kirk E S The acti e and pa ive components of extravascular coronary resi t ance Cardiovasc Res 9 161 1975
18 L Abbate A Mildenberger R R Chri tie L McGre gor M and Kla sen G A The role of coronary perfu ion pres ure and left ventricular intracavitary pres ure a determinants of coronary blood flow distribu tion Fed Proc 33 414 1974
19 Ross J Jr Waldhausen J A and Braunwald E Studies on digitalis I Direct effects on peripheral vascular resi tance J Clin Invest 39 930 1960
20 Mason D T, and Braunwald E Studies on digitalis X Effect of ouabain on forearm vascular resistance and venous tone in normal subjects and patients in heart failure J Clin Invest 43 532 1964
21 Vatner S F Higgins, C B Franklin D and Braun wald E Effects of a digitalis glyco ide on coronary and y temic dynamics in conscious dogs Circ Res 28 470 1971
22 Hamlin N P, Willerson J T Garan H and Powell W J Jr The neurogenic va ocon trictor effect of digitalis on coronary vascular resi tance J Clin Invest 53 288 1974
23 Garan H Smith T W and Powell W J Jr The central nervous y tem a a site of action for the coronary va ocon trictor effect of digoxin J Clin Invest 54 1365 1974
24 Doster M P and Scott J B Effect of diphenylhydan toin on coronary resi tance and myocardial contractile force before and after ouabain Am Heart J 87 761 1974
25 Rahimtoola S H and Gunnar R M Digitalis in acute myocardial infarction help or hazard Ann Intern Med 82 234 1975
26 Maroko P R Kjek hus J K, Sobel B D Watanabe T Covell J W Ross J Jr and Braunwald E Factors influencing infarct size following experimental coronary artery occlu ion Circulation 43 6 1971
27 Rahimtoola S H Sinno M Z Chuquimia P Loeb H S Rosen K M and Gunnar R M Effects of ouabain on impaired left ventricular function in acute myocardial infarction N Engl J Med 287 527 1972

The arrhythmogenic effect of static electricity on the dog heart*†

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The explosive growth of electronic gadgetry in medicine has been accompanied by ever increasing electrical hazards to patients and staff The existence of such hazards has been known for years, but only recently has there been attention focused on this problem at the bedside level An ad hoc committee appointed by the Intersociety Commission, investigated the problem and made recommendations for electrical safety encompassing the entire electronic environment in critical care areas [1] Improved manufacturing standards continuing programs of medical maintenance and intensive education of personnel involved with electronic equipment were stressed

In this report,[1] the potential hazard of static electricity was mentioned It was stated that static charges could induce fatal arrhythmias [2] but no firm evidence was presented to establish this claim Nonetheless the recommendation was made that carpet not be placed in critical care areas in order to minimize static charges In an effort to substantiate the validity of this recommendation we undertook an investigation of the cardiac effects of static electricity Our results demonstrated that cardiac rhythms could be altered in everyday situations and provided evidence which supports the committee s recommendations

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†The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense

Material and methods

Seven mongrel dogs, weighing between 8 to 15 kilograms were anesthetized with pentothal and maintained on continuous fluothane anesthesia with respiratory support * A No 5 bipolar pacing catheter was placed in the right ventricle of the dogs through a cutdown over the left jugular vein Each animal was continuously monitored electrocardiographically Catheter position indicating good endocardial contact was verified by an injury current recorded from the distal electrode A Medtronics portable pacing unit was used to establish the pacing threshold All dogs could be paced at less than 1 mamp (which was calculated to represent approximately one microjoule of delivered energy)

Static electrical charges were then generated by shuffling our shoed feet over synthetic or wool carpet Static charges were discharged from the fingertips and measured through a 50 1 megohm resistor into a Tektronix storagescope (Type 564B with 3A6 dual trace vertical amp and 3B3 time base) (Fig 1) More than one spike ie, 'double static discharge (Fig 2 *A* and *B*) was induced occasionally by incomplete initial contact with the catheter tip Similar static charges were then applied directly on the external end of the pacemaker wire leading to the distal electrode within the right ventricle The effect of the current on the heart rhythm was continuously monitored on the surface electrocardiograph (ECG) By repetitive trial, charges were introduced during all phases of the cardiac cycle

This procedure was performed in four normal dogs and the experimental plan was repeated in three dogs in whom acute myocardial infarction was induced by open chest ligation of the circum

The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care

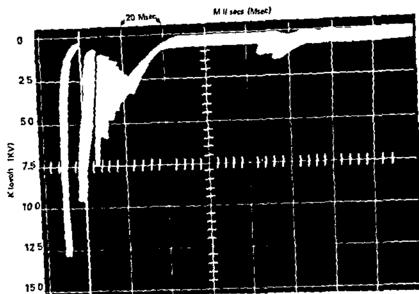


Fig 1 Represents the wave form of a typical static discharge with notable ringing in evidence There were 12 5 KV generated and a spark was noted at the moment of discharge Calibration factors are 2.5 KV per division vertically and 20 msec per division horizontally

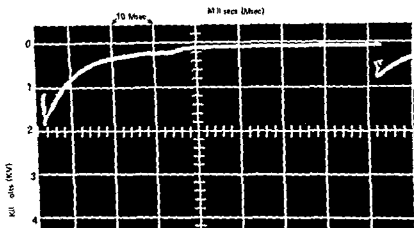


Fig 2A The waveform of a double static discharge illustrates the time between the first and the second discharges The first discharge represents approximately 2 KV and the second discharge approximately 1 KV Neither of these were perceptible to the generating person The double discharge resulted from incomplete contact when the pacing catheter was first touched followed in 80 msec. by completion of the discharge

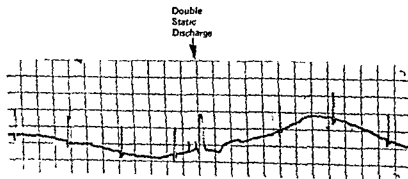


Fig 2B A double static discharge Note two spikes under the arrow 0 09 second apart The first spike occurs in the relative refractory period and does not pace The second spike however results in a paced beat.

The arrhythmogenic effect of static electricity on the dog heart*†

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The explosive growth of electronic gadgetry in medicine has been accompanied by ever increasing electrical hazards to patients and staff The existence of such hazards has been known for years, but only recently has there been attention focused on this problem at the bedside level An ad hoc committee appointed by the Intersociety Commission, investigated the problem and made recommendations for electrical safety encompassing the entire electronic environment in critical care areas[1] Improved manufacturing standards, continuing programs of medical maintenance, and intensive education of personnel involved with electronic equipment were stressed

In this report,[1] the potential hazard of static electricity was mentioned It was stated that static charges could induce fatal arrhythmias,[2] but no firm evidence was presented to establish this claim Nonetheless, the recommendation was made that carpet not be placed in critical care areas in order to minimize static charges In an effort to substantiate the validity of this recommendation we undertook an investigation of the cardiac effects of static electricity Our results demonstrated that cardiac rhythms could be altered in everyday situations and provided evidence which supports the committee s recommendations

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†The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Departm nt of Defense

Material and methods

Seven mongrel dogs weighing between 8 to 15 kilograms, were anesthetized with pentothal and maintained on continuous fluothane anesthesia with respiratory support * A No 5 bipolar pacing catheter was placed in the right ventricle of the dogs through a cutdown over the left jugular vein Each animal was continuously monitored electrocardiographically Catheter position indicating good endocardial contact was verified by an injury current recorded from the distal electrode A Medtronics portable pacing unit was used to establish the pacing threshold All dogs could be paced at less than 1 mamp (which was calculated to represent approximately one microjoule of delivered energy)

Static electrical charges were then generated by shuffling our shoed feet over synthetic or wool carpet Static charges were discharged from the fingertips and measured through a 50 1 megohm resistor into a Tektronix storagescope (Type 564B with 3A6 dual trace vertical amp and 3B3 time base) (Fig 1) More than one spike i e double static discharge' (Fig 2 *A* and *B*) was induced occasionally by incomplete initial contact with the catheter tip Similar static charges were then applied directly on the external end of the pacemaker wire leading to the distal electrode within the right ventricle The effect of the current on the heart rhythm was continuously monitored on the surface electrocardiograph (ECG) By repetitive trial, charges were introduced during all phases of the cardiac cycle

This procedure was performed in four normal dogs and the experimental plan was repeated in three dogs in whom acute myocardial infarction was induced by open chest ligation of the circum

The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care

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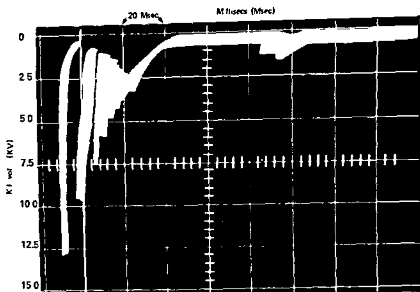


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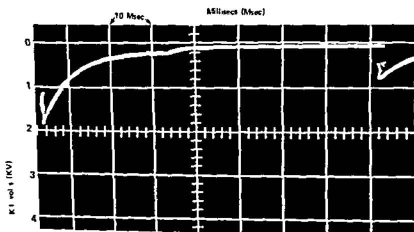


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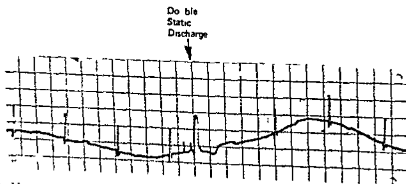


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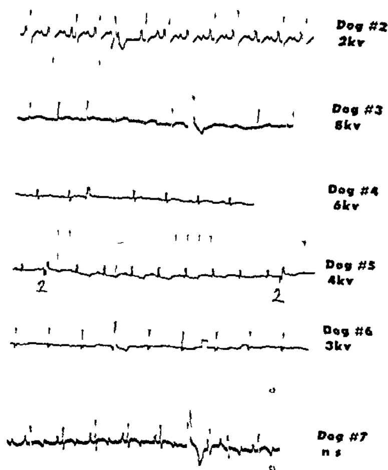


Fig 3 Static discharges above 2 KV (the approximate level of perception to the generating person) uniformly resulted in paced beats unless delivered in the absolute refractory period Note however that a paced beat also occurred in Dog No 7 when no sensation (NS) was felt by the generating person This was not an uncommon occurrence The KV of each impulse illustrated represents an estimate

flex branch of the left coronary artery Static charges were also delivered directly into the infarcted area by a metal needle

Results

Quantification of electrical energy The voltage of static charges reached 22 000 volts The charges varied with the shoes* worn type of rug duration of shuffling, and the day—presumably related to temperature humidity, etc The perceptible level of shock to the finger was established at two to three thousand volts The energy delivered, as measured through the 50 1 megohm resistor, was calculated at 4 3 millijoules (4300 microjoules) for an 8,000 volt discharge Resistance of the pacing wire and intervening tissues from the right ventricle to the ground lead were measured on a calibrated Simpson meter at 10,000 to 50 000 ohms The amount of delivered energy through this lower resistance pathway within the dogs was considered identical to that measured through the 50 1 megohm resistor into the storage scope

The effect of static charges on the heart rhythm of the normal dogs Static discharges exceeding 2,000 volts uniformly resulted in paced beats unless delivered in the absolute refractory period (Fig 3) Ventricular beats were often initiated by discharges below the level of perceptible shock (Fig 3 dog No 7) In fact, a single gliding movement of one s foot across the rug generated a sufficient charge to pace the heart. This allowed repetitive pacing at rates nearing 60/min (Fig 4) Powerful shocks delivered in the vulnerable period of the cardiac cycle did not produce repetitive tachyarrhythmias (Fig 5)

The effect of static charges on heart rhythm of dogs with acute myocardial infarction The results obtained in the first two dogs were essentially the same results that were obtained in the normal dog In the third dogs however a static discharge approximating 6 000 volts clearly initiated ventricular fibrillation (VF) (Fig 6) This appears to have resulted from a double discharge in which current was repetitively delivered after the initial discharge had produced a ventricular premature beat (VPB) This secondary shock occurred within the vulnerable period of the VPB (note the deformity of the terminal part of the T wave) and initiated VF Electrical countershock returned the rhythm to sinus At no time before nor immediately after were any spontaneous premature beats evident Placement of the static charge directly into the area of infarction by a metal needle, resulted in no pacemaker activity whatsoever

Discussion

It has been established that electrical energy of minute proportions (1 microjoule) may result in cardiac pacemaker function [3]

We established that the single gliding movement of one s foot across the rug generated a sufficient charge to pace the heart and in event of battery failure repetitive gliding could conceivably serve as an energy source

Alternating current as small as 20 microamps for periods of 2 seconds representing 4 400 microjoules of energy has resulted in VF in dogs [4] In

* Shoes had to be a type which would create measurable friction foot coverings such as operating room bootie did not generate enough energy to quantitate

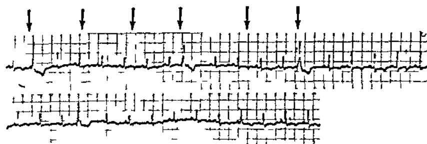


Fig 4 The arrows indicate static discharges recorded as spikes on the surface ECG They occur at approximately 60 times per minute No pacing occurs when the spikes fall in the refractory period of normally conducted beats.

contrast direct currents of 35 mamp for only 2 msec representing 1 000 microjoules has been the average amount of energy required to produce VF when delivered during the vulnerable period [5] In diseased hearts the fibrillatory threshold is significantly lower [6] Indeed VF has been initiated by the minute energy of a battery operated pacemaker when delivered within the vulnerable period [7] In this instance assuming a maximum 9 volt battery output the actual energy initiating VF would have been 36 microjoules

It is not surprising therefore that the energy levels generated by static charges (in the range of several thousand microjoules) can result in pacemaker function and VF One might wonder why VF was not produced more regularly when these levels of energy were delivered within the vulnerable period The probable explanation revolves around the short duration of peak energy in the decaying wave form of static discharges This contrasts sharply with the longer square wave form of direct current

One explanation for the occurrence of VF in one dog and not in any of the other dogs in which similar charges were delivered well within the vulnerable period relates to the lowered fibrillatory threshold of early VPBs A prime determinant of fibrillatory threshold is the temporal dispersion of recovery of excitability which is greater in early premature beats than in beats originating in fully excitable tissue Furthermore it has been established that the effect of prematurity on the fibrillation threshold is greatest at points near the sight of origin of the premature response In our case the discharge giving rise to the VPB and the subsequent secondary discharge were delivered at the identical site accounting for a substantial reduction in the fibrillatory threshold

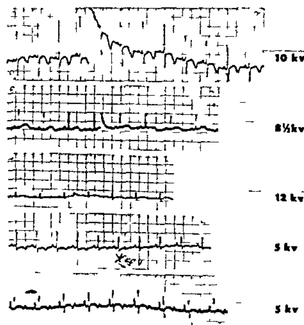


Fig 5 Static discharges in the range of 5 to 12 KV even when delivered in the vulnerable period did not produce repetitive tachyarrhythmias in any of the normal animals.

Summary

Seven dogs three with surgically induced acute myocardial infarction were subjected to the effects of static electricity discharged from our fingertips onto the external end of a transvenous right ventricular pacemaker Initiation of ventricular beats occurred regularly when shocks were perceptible to the generating person and not infrequently when energy levels were below perception In one dog with myocardial infarction ventricular fibrillation was clearly related to the static discharge

The data obtained in this study support the recommendations of the Electrical Safety Hazard



Fig 6 Static discharges approximating 6 KV were generated resulting in VPBs On the third occasion this was followed by ventricular *tachycardia* which rapidly degenerated into VF The explanation we feel lies in the double discharge (see *Figs 2A* and *B*) which is manifest in the T wave of the paced beat (*compare the T wave of the third paced beat with that of the other two*)

Committee that critical care areas not be carpeted in order to minimize static charges In addition to low static floor covering in these areas, one can reduce static charge by the use of foot coverings such as those worn in the operating room We found that no static charge could be developed when wearing the expandable operating room 'booties Since static charges were transmitted through our fingertips, probably the best means of protecting the electrically sensitive patient against the hazard of static electricity is to instruct personnel to wear rubber gloves whenever direct contact with the external ends of a pacing catheter becomes necessary Routinely such exteriorized pacemaker ends should also be covered with a nonconductive substance

We would like to thank the personnel of the Department of Medical Research and Development Veterinary Medicine Service and Medical Maintentance Branch for their cooperation and enthusiastic support In particular Dr Lee Chenault V C Mr Charles Salsman Mr Clinton Winstead and Mr Richard Costa are to be commended

REFERENCES

1 Electronic equipment in critical care areas Report of the Intersociety Commission for Heart Disease Resources, Circulation 44 A 237 1971
2 Walter C H (ed) Electrical hazards in hospitals Washington DC 1970 National Academy of Sciences
3 Lown B Klein M D and Hershberg P I Coronary and precoronary care Am J Med 46 ,05 1969
4 Whalen R E Starmer F and McIntosh H D Electrical hazards associated with cardiac pacemaking Ann N Y Acad Sci 111 922 1963 64
5 Widman W D Eisenberg L Levilsky S Mauro A and Glenn W W Ventricular fibrillation complicating electrical pacemaking a comparison of direct current and radiofrequency cardiac pacemaker stimulation Surg Forum 14 260 1963
6 Phibbs C M Levy L M and Maclean L D The influence of temperature and coronary occlusion on the ventricular fibrillation threshold Surg Gynecol Obstet 109 216 19_9
7 Bilitch M Cosby R S and Cafferky E A Ventricular fibrillation and competitive pacing N Engl J Med 276 598 1967
8 Han J and Moe G K Nonuniform recovery of excitability in ventricular muscle Circ Res 14 44 1964
9 Han J DeJalon G and Moe G K Fibrillation threshold of premature ventricular responses Circ Res 18 18 1966

Horseshoe lung: Report of two cases

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In the scimitar syndrome congenital anomalies of the lungs and the cardiovascular system are usually associated. Recently Dische and associates[6] presented a variant of this syndrome, one that displayed fusion of the right and left lower lobes of the lungs in a "horseshoe" fashion. This defect was in addition to the usual features of right lung hypoplasia, dextroversion of the heart,* partial anomalous pulmonary venous return from the right lung to the inferior vena cava (IVC) (the scimitar shadow on anteroposterior chest roentgenogram), and the aberrant systemic arterial supply to the same lung. Spencer described the only other known case of horseshoe lung. The diagnosis in both Dische's and Spencer's cases was made from autopsy findings. This report presents two cases of horseshoe lung. Both patients underwent successful surgical repair.

Case reports

Case 1. A seven-year-old girl was admitted to the Texas Children's Hospital for diagnostic studies. Her mother had received cortisone therapy for bronchial asthma during the second, third, and seventh months of pregnancy. The patient was born at term after normal labor and delivery. Difficulty in swallowing occurred at three months of age when dextrocardia was recognized. Angiographic studies were done at the age of two and one-half years but were not available for review. The patient had been troubled with frequent bronchitis since infancy but no cardiovascular symptoms were present.

Upon admission of the patient, pertinent physical findings included blood pressure of 120/60 mm Hg, pulse rate of 80 beats per minute, and respiratory rate of 22 per minute. Cyanosis was not present. The chest was asymmetrical because of hypoplasia of the right hemithorax. The apical impulse of the heart was felt in the fifth right intercostal space at the anterior axillary line. A right parasternal lift was present. The second sound was fixedly split and followed by a rumble at the apex. The liver was palpated at the right costal margin. Chest roentgenography confirmed that the cardiac shadow was shifted to the right, the right hemithorax was smaller than the left, and the left hilar vessels were prominent. A scimitar shadow could be recognized (Fig. 1). The electrocardiogram was consistent with dextroversion. Evidence from a lung scan indicated ventilation and perfusion of the right lower lobe to be decreased, and a large triangular-shaped defect at the base of the right lung was noted. Percutaneous venous cardiac catheterization revealed situs solitus of the viscera and the atria with atrioventricular concordance and normally crossed great vessels. An oxygen saturation step-up at the atrial level was noted. An atrial septal defect was passed with the catheter. The pulmonary artery pressure was moderately increased to 50/18 mm Hg. The pulmonary to systemic flow ratio (Qp/Qs) was calculated to be 6/1. Pulmonary angiography showed branches of the right pulmonary artery crossing the midline and reaching the lower medial portion of the left hemithorax (Fig. 2). A single pulmonary venous trunk was visualized to drain the entire right lung into the IVC at the junction with the right atrium (Fig. 3). An aberrant artery arising from the abdominal aorta and reaching the right lower lobe through the diaphragm was not recognized preoperatively, although in retrospect it could have been tracked following the left ventriculogram. The preoperative diagnosis included scimitar syndrome with hypoplasia of the right lung and possible horseshoe lung, dextroversion of the heart, anomalous pulmonary venous return from the right lung into the IVC, and atrial septal defect.

The child underwent surgery on August 9, 1974. The right lung was explored carefully and found to be free of scissurae and confluent with the left lung in the retrocardiac space, thus forming a "horseshoe" structure. Also, two systemic arteries were found to reach the lower part of the right lung through the diaphragm. A right pneumonectomy was performed and

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*Dextroversion is defined as a congenitally anomalous positioning of the heart in which the situs of the viscera and atria is solitus and the cardiac apex is to the right.



Fig 1 Case 1 Posteroanterior chest film shows the cardiac shadow in the right hemithorax which is smaller than the left The left hilar vessels are prominent A scimitar shadow is superimposed with the cardiac silhouette



Fig 2 Case 1 Pulmonary arteriogram shows branches of the right pulmonary artery crossing the midline and reaching the lower medial portion of the left hemithorax

an atrial septal defect of moderate size located in the fossa ovalis was closed using a Dacron patch Postoperative recovery was excellent and the child was discharged on August 19 1974 Pathologic study of the specimen disclosed inferomedial consolidation of the right lung and confirmed the absence of lobar scissurae

Case 2 A four month old girl was born after a normal pregnancy and delivery At the age of two months she was noted to experience wheezing and labored respiration and responded to bronchodilators At three months of age she relapsed into respiratory distress and was hospitalized elsewhere Chest roentgenography showed evidence of dextrocardia and opacification of the entire right hemithorax Bronchography cardiac catheterization and exploratory thoracotomy were performed but the underlying defects remained unclarified The child continued to do poorly and was transferred to our institution

When admitted the patient was in moderate respiratory distress The respiratory rate was 60 per minute the systolic blood pressure was 60 mm Hg and the heart rate was 150 beats per minute Mild cyanosis was noted Intercostal retractions were present The right hemithorax was dull on percussion and breathing sounds were decreased while the left hemithorax was hyperresonant The heart was palpated on the right side of the chest No heart murmur was recognized The electrocardiogram showed evidence of right ventricular hypertrophy and right axis deviation On the chest roentgenogram the right hemithorax was almost completely opacified the pulmonary vascular markings were increased in the left lung and a well defined inferomedial area of emphysema was identified on the left (Fig 4) The heart and mediastinum were shifted to the right Ventilation and perfusion scans of the lungs demonstrated asymmetrical distribution of the radioactive material with almost total absence of ventilation of the right lung Mild air trapping was present in the left lower base The perfusion of the right lung was notably diminished Cardiac catheterization and angiographic studies demonstrated evidence of situs solitus of the viscera atrioventricular concordance and normally crossed great vessels The pulmonary arterial pressure was 72/20 mm Hg mean 40 Oxygen saturations indicated evidence of a left to right shunt at the atrial level Pulmonary venous oxygen desaturation (? per cent) was found and corrected by O mask breathing Q Qs was calculated to be 2 5/1 A patent foramen ovale and a large ductus arteriosus were entered A lower branch of the right pulmonary artery was noted to cross the midline and to reach the lower lobe of the left lung (Fig 5) The same lobe and the right lower lobe were also reached by branches of a vessel originating from the abdominal aorta (Fig 6) During the venous phase of the angiogram a large channel appeared that emptied directly at the lower atriocaval junction The diagnosis included scimitar syndrome with hypoplasia of the right lung dextroversion of the heart anomalous right pulmonary venous return into the IVC emphysematous horseshoe lung aberrant systemic arterial supply of the right lower lobe and of the aberrant left lobe a patent foramen ovale patent ductus arteriosus and pulmonary hypertension with moderately increased pulmonary flow The diagnosis of horseshoe lung was confirmed at surgery which consisted of a right pneumonectomy and division and ligation of the ductus The bronchial and arterial supplies of the horseshoe lung were ligated Pathological examination of the specimen confirmed that the lung was consolidated Microscopic examination showed an increased amount and irregular arrangement of the bronchioli and of the interstitial connective tissue where the unusual presence of striated muscle fibers was noted Postoperative recovery of the patient initially was complicated by a right hemothorax and atelectasis (or infarction) of the left lower lobe however the child was discharged on the eleventh day after surgery in good condition



Fig 3 Case 1 The venous phase of the pulmonary angiogram shows a single pulmonary venous trunk that drains the entire right lung into the IVC at the junction with the right atrium

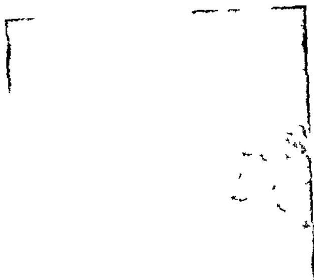


Fig 4 Case 2 The right hemithorax is almost completely opacified in this preoperative chest film The left hemithorax shows increased vascular markings and a well defined inferomedial area of emphysema The heart and mediastinum are shifted to the right

Discussion

Horseshoe lung is a term used for an unusual malformation of the lungs similar to the more frequent anomalies of other paired viscera (i e horseshoe kidneys or suprarenal glands)

The term was introduced in the literature by Spencer who did not describe in detail his observation Dische and associates provided the only previous full report on the subject Our patients like that reported by Dische had a number of other anomalies along with the horseshoe lung—e g dextroversion of the cardiac apex anomalous return of most of the right pulmonary veins to the IVC or its junction to the right atrium aberrant systemic arterial supply of parts of the lungs (most frequently the lower lobe of the right lung) and hypoplasia of the right lung More cases should be studied before a final conclusion can be made regarding the occurrence of the horseshoe lung only in association with the scimitar syndrome Our review of all autopsy reports at the Texas Children s Hospital (1955 to 1975 4 088 patients) failed to reveal any other example of horseshoe lung either isolated or in association with the scimitar syndrome (one case)

According to the present status of knowledge this complex of anomalies would indicate that the basic embryologic error occurs in a very early stage of development when the pleuropericardial and pleuroperitoneal folds form and fuse to define the mediastinum and the diaphragm Normally the cephalic portion of the coelomatic cavity contains the heart primordia and the lung buds As the lung buds grow the coelomatic cavity divides partially in pleural spaces containing the lung buds and the pericardial space Still communications persist between the pleura and the pericardium and the pleura and the peritoneal cavity (pleuropericardial and pleuroperitoneal channels respectively) before the septum transversum develops These channels eventually disappear by fusion of the pleuropericardial and pleuroperitoneal folds From this stage the lungs are completely separated by the mediastinal structure and the anomalous development of horseshoe lung would not be possible

It is very probable that the other anomalies of the complex (hypoplasia of the right lung partial anomalous pulmonary venous return and dextroversion of the cardiac apex) occur later in the development of the embryo One can postulate that the first anomaly to appear in the complex malformation is the horseshoe lung The anomalous morphogenesis should consist of the persistence of a communication between the two pleural spaces behind the heart with growth of the posteroinferior lobe of the right lung into the left pleural space This would cause the remaining right lung to be hypoplastic and promote the



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is suspected or proved selective right pulmonary artery (or main pulmonary artery) angiography should be made to visualize the distal branching In the horseshoe lung the pulmonary artery of the anomalous lobe originates from the right pulmonary artery and crosses the mediastinum to reach the lower and posterior portion of the left chest Bronchography is neither a necessary nor advisable procedure in this condition but could be indicated sometimes by the frequent presentation of recurrent severe pulmonary infections in these patients Bronchography could demonstrate evidence of bronchial branches crossing the midline to reach the anomalous lobe

4 *Diagnosis of aberrant systemic arterial supply to the lungs* This diagnosis can only be made by abdominal aortography

5 *Clinical course and management* The horseshoe lung syndrome predisposes to pulmonary disease and the patient may present with recurrent respiratory infections and/or emphysema of the anomalous lobe Whenever associated heart anomalies cause important cardiovascular overloading or the lung impairment is severe surgical treatment is to be considered

In our patients we elected to perform pneumonectomy of the right lung and ligation of the pulmonary systemic and bronchial supply to the anomalous lobe A median sternotomy was preferred because of associated heart anomalies The anomalous lobe was found adherent to the adjacent structures without pleural cavity and was left in place in our two cases An ischemic infarction is the necessary consequence of this procedure Both patients tolerated well the pneumonectomy and even if chest asymmetry and dorsal spine scoliosis became worse the patients have fairly normal cardiorespiratory capacities one year after operation

Summary

Two cases of horseshoe lung are described one was suspected and the other was diagnosed preoperatively Both underwent successful surgical treatment The embryology of this anomaly is briefly reviewed with reference to the closely related scimitar syndrome (anomalous venous return of right lung to inferior atriocaval junction) Diagnostic studies are discussed with stress on the need for a thorough functional evaluation of both the heart and lungs before the surgical indication is made

REFERENCES

1 Neill, C A. Ferencz, C Sabiston D C and Sheldon, H The familial occurrence of hypoplastic right lung with systemic arterial blood supply and venous drainage (Scimitar syndrome") Bull. Johns Hopkins Hosp 107 1 1960
2. Kuiper Oosterwal, C H., and Moula rt A The scimitar syndrome in infancy and childhood Eur J Cardiol. 1 ? 1973
3 Mathey J Galey J J Logeais, Y., Santoro E Vanetti, A., Maurel A and Wuerflein R Anomalous pulmonary venous return into inferior vena cava and associated bronchovascular anomalies (the scimitar syndrome) Thorax 23 398 1968
4 Farnsworth, A E., and Ankeney J L. The spectrum of the scimitar syndrome J Thorac Cardiovasc Surg 68 37 1974
5 Kiely B Filler J Stone S and Doyle E F Syndrome of anomalous venous drainage of the right lung to the inferior vena cava Am. J Cardiol. 20 102 1967
6 Dische M R Teixeira M L., Winchester P H and Engle M A Horseshoe lung associated with a variant of the scimitar syndrome Br Heart J 36 617 1974
7 Spencer H Pathology of the lung 2nd ed., Oxford 1968 Pergamon Press, Inc p 7?
8. Patten B M Human embryology New York 1968 McGraw Hill Book Company Inc p 399
9 Castro-Quezada, A Nadal Ginard B and de la Cruz M V Experimental study of the formation of the bulboventricular loop in the chick J Embryol Exp Morphol 27 6?3 19?
10 Leachman R D Angelini, P and Cokkinos D Hepato-atrial dissociation Report of two cases and clinical implications Chest 63 976 1973
11. Momma K and Linde L M Cardiac rhythms in dextrocardia Am J Cardiol. 25 4?0 19?0



Fig 5 Case 2 Pulmonary angiogram shows a lower branch of the right pulmonary artery crossing the midline to reach the lower portion of the left chest



Fig 6 Case 2 Aortogram shows the aberrant systemic arterial supply of the right lower lobe and of the anomalous lobe from the abdominal aorta

displacement of the cardiac apex to the right. In this set of circumstances the occurrence of partial anomalous pulmonary venous return possibly is related to the altered tropism of the right pulmonary veins because of the existing pleuro pulmonary anomalies and the dextroversion of the heart

These speculative deductions while offering a unitary explanation of this complex anomaly are proposed as an incentive to experimental embryologists to study the normal and abnormal development of the pleuropericardial folds There is little experimental knowledge on this subject but preliminary studies by Castro Quezada and associates[9] appear to indicate a prominent role of these coelomatic structures as inductors of the heart tube looping

Clinically, a few points should be emphasized The diagnosis of this complex anomaly is neither obvious nor apparent in routine studies Our experience would suggest a logical sequence of investigations

1 *Radiographic diagnosis of dextroversion* The presence of most of the heart shadow in the right chest in the presence of right sided liver is good evidence of dextroversion[10] that can be supported by electrocardiographic evidence of situs solitus atrialis[11]

2 *Diagnosis of partial anomalous pulmonary venous return* The radiographic appearance of a scimitar like structure behind the heart shadow or to the right of it is a well known sign Manipulation of the catheter into this structure from the IVC is a definite diagnostic clue at the time of cardiac catheterization

3 *Diagnosis of horseshoe lung* Only unusual cases can be recognized or suspected from radiographic evidence We refer to patients with dextroversion and scimitar syndrome in whom radiolucency or consolidation of the segment of the right lung that prolapses into the left chest are present The lung area that is then defined would be suggestive of a horseshoe lung It is interesting to note that a differential diagnosis discussed in our second case was that of an absent right pericardium In fact the radiolucency of the anomalous lobe (emphysematous) simulated the pericardial sac while the heart shadow was on the right side The definite diagnosis of horseshoe lung can only be made by angiography or bronchography In any case of dextroversion especially if the scimitar syndrome

is suspected or proved selective right pulmonary artery (or main pulmonary artery) angiography should be made to visualize the distal branching In the horseshoe lung the pulmonary artery of the anomalous lobe originates from the right pulmonary artery and crosses the mediastinum to reach the lower and posterior portion of the left chest Bronchography is neither a necessary nor advisable procedure in this condition but could be indicated sometimes by the frequent presentation of recurrent severe pulmonary infections in these patients Bronchography could demonstrate evidence of bronchial branches crossing the midline to reach the anomalous lobe

4 *Diagnosis of aberrant systemic arterial supply to the lungs* This diagnosis can only be made by abdominal aortography

5 *Clinical course and management* The horseshoe lung syndrome predisposes to pulmonary disease and the patient may present with recurrent respiratory infections and/or emphysema of the anomalous lobe Whenever associated heart anomalies cause important cardiovascular overloading or the lung impairment is severe surgical treatment is to be considered

In our patients we elected to perform pneumonectomy of the right lung and ligation of the pulmonary systemic and bronchial supply to the anomalous lobe A median sternotomy was preferred because of associated heart anomalies The anomalous lobe was found adherent to the adjacent structures without pleural cavity and was left in place in our two cases An ischemic infarction is the necessary consequence of this procedure Both patients tolerated well the pneumonectomy and even if chest asymmetry and dorsal spine scoliosis became worse the patients have fairly normal cardiorespiratory capacities one year after operation

Summary

Two cases of horseshoe lung are described one was suspected and the other was diagnosed preoperatively Both underwent successful surgical treatment The embryology of this anomaly is briefly reviewed with reference to the closely related scimitar syndrome (anomalous venous return of right lung to inferior atriocaval junction) Diagnostic studies are discussed with stress on the need for a thorough functional evaluation of both the heart and lungs before the surgical indication is made

REFERENCES

1 Neill, C A Ferencz C Sabiston D C and Sheldon, H The familial ocrurrence of hypoplastic right lung with systemic arterial blood supply and venous drainage (Scimitar syndrome") Bull Johns Hopkins Hosp 107 1 1960
2 Kuiper Oosterwal, C H., and Moulaert A The scimitar syndrome in infancy and childhood Eur J Cardiol. 1 55 1973
3 Mathey J Galey J J., Logeais, Y., Santoro E., Vanetti, A., Maurel, A. and Wuerflein R Anomalous pulmonary venous return into inferior vena cava and associated bronchovascular anomalies (the scimitar syndrome) Thorax 23 398 1968
4 Farnsworth A E and Ankeney J L. The spectrum of the scimitar syndrome J Thorac Cardiovasc Surg 68 37 1974
5 Kiely B Filler J Stone S and Doyle E F Syndrome of anomalous venous drainage of the right lung to the inferior vena cava Am J Cardiol. 20 102, 196
6 Dische M R Teixeira M L., *Winchester P H.*, and Engle M A Horseshoe lung associated with a variant of the "scimitar" syndrome Br Heart J 36 617 1974
7 *Spencer H* Pathology of the lung 2nd ed Oxford 1968 Pergamon Press Inc p 72
8 Patten B M Human embryology New York 1968 McGraw Hill Book Company Inc., p 399
9 Castro-Quezada, A Nadal Ginard B and de la Cruz M V Experimental study of the formation of the bulboventricular loop in the chick, J Embryol Exp Morphol 27 623 19 ?
10 Leachman R. D Angelini P., and Cokkinos D Hepato atrial dissociation Report of two cases and clinical implications, Chest 63 976 19 3
11 Momma K., and Linde L. M Cardiac rhythms in dextrocardia Am J Cardiol 25 420 19 0

Inferior vena cava tumor thrombus extending into the right atrium and mimicking right atrial myxoma Angiographic differentiation

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Atrial myxoma is the most frequent primary cardiac tumor[1] Twenty five per cent of myxomas occur in the right atrium[1] as of 1972 a review of the literature revealed successful surgical extirpation in 40 cases of right atrial myxoma[2] The widespread use of echocardiography has increased interest in these tumors and numerous reports of diagnosis of both left[3,4] and right atrial myxomas have appeared The definitive diagnosis is usually made by angiography[6]

It is well for the clinician to remember however that metastatic or secondary cardiac tumors occur 20 to 40 times as frequently as primary cardiac tumors[1] We report a case of recurrent hypernephroma with tumor thrombosis of the inferior vena cava (IVC) extending directly into the right atrium The distal portion of the tumor mass in the right atrium displayed marked cineangiographic mobility simulating a right atrial myxoma

Case report

A 61 year old woman was referred to the University of Iowa Hospital for evaluation of progressive weakness dyspnea and chest pain of 1 year s duration Five years previously she had undergone removal of the right kidney for a hypernephroma no evidence of metastasis or extension was present at that time Initial investigation of her current complaints had considered the possibility of tumor recurrence but no specific evidence of this had been found an intravenous pyelogram showed absence of the right kidney and collecting system upper gastrointestinal gallbladder and barium enema x rays were normal

Physical examination revealed a chronically ill woman in no acute distress The jugular pulse showed a prominent a wave There was dullness at the right lung base The precordium was quiet an early systolic click was heard at the apex No murmurs or diastolic gallops were heard A well healed flank scar was present but no abdominal or flank tenderness or masses There was no edema

A chest x ray revealed a right pleural effusion the cardiac size and contour were normal An electrocardiogram (ECG) showed nonspecific ST T changes An echocardiogram revealed normal mitral valve motion the aortic tricuspid and pulmonic valves could not be adequately visualized A phonocardiogram confirmed the presence of an early systolic click no diastolic sounds were recorded

A bone scan and bone marrow biopsy were normal Thoracentesis yielded clear amber fluid no tumor cells were present The bilirubin was 1 6 mg per 100 ml a liver scan was consistent with hepatocellular disease

Cardiac catheterization was undertaken because of her complaints of dyspnea and chest pain The mean right atrial pressure was 7 mm Hg with a prominent a wave of 14 mm Hg a v wave of 6 mm Hg and a normal y descent The right ventricular pressure was 24/4 mm Hg the contour of the right ventricular pressure wave was normal without a notch on the upstroke The pulmonary artery pressure was 16/8 mm Hg and the mean pulmonary artery wedge pressure was 5 mm Hg

Angiographic findings Angiographic contrast medium injection into the right atrium revealed a large lobulated mass the tip of which prolapsed across the tricuspid valve into the right ventricle in diastole (Fig 1) The mass appeared to be attached inferiorly although the radiographic dye refluxed superiorly into the superior vena cava none was seen to reflux inferiorly into the IVC (Figs 1 and 2) suggesting obliteration of the IVC Injections of angiographic dye into both iliac vein confirmed this in both cases the dye column appeared to terminate abruptly before the site where the two iliac veins normally join to form the IVC and the cava never opacified (Fig 3) Collateral vessel extending superiorly into the abdomen were present

The patient tolerated the procedure without difficulty However her subsequent hospital course was one of rapid deterioration and she died 2 weeks after the catheterization

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Fig 1 Right atrial cineangiogram power injection of 30 c c of angiographic contrast material A multilobular mass (arrows) fills the right atrium (*RA*) in systole (panel *A*) and prolapses through the tricuspid valve into the right ventricle (*RV*) in diastole (panel *B*) Dye refluxes into the superior vena cava (*SVC*) but no dye appears in the inferior vena cava The location of the inferior vena cava–right atrial junction is marked by the open arrow

Autopsy confirmed the presence of a large tumor thrombus which filled the IVC (Fig 4) and extended well into the right atrium (Fig 5)

Discussion

The angiographic finding of an atrial mass prolapsing across the atrioventricular valve with each cardiac cycle is characteristic of an atrial myxoma[6] In this case however the appearance of a right atrial myxoma was mimicked by the distal end of the tumor thrombus which was lying relatively free in the atrial cavity and thereby displayed motion similar to a myxoma An important angiographic clue to the correct diagnosis was the failure of the contrast material to reflux into and outline the IVC while at the same time the superior vena cava was clearly seen A review of the angiograms of published cases of right atrial myxoma shows that the IVC should be visible on right atrial injections This is expected since almost all myxomas attach to the fossa ovalis and thereby should not occlude the atrial caval junction

Occlusion of the IVC was confirmed in this case by iliac vein injections of contrast material This should be done if the atrial injection raises any suspicion of a tumor extending into the atrium from the IVC When a right atrial myxoma is suspected right atrial angiography may be hazardous because of the possibility of dislodging clot or tumor resulting in pulmonary emboli[4] such an incident appears to have occurred in the patient reported by Glazer and associates[3] Steiner[4] suggested that superior vena caval injections should be used instead of right atrial injections to avoid this complication If this is done the IVC may not be visualized even when patent



Fig 2 Right atrial cineangiogram A hand injection of 10 c c of angiographic contrast material into the low right atrium outlines the mass (closed arrows) but fails to opacify the inferior vena cava The location of the inferior vena caval atrial junction is marked by an open arrow

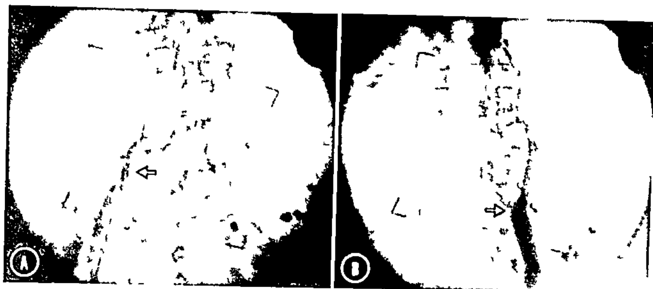


Fig 3 Iliac venograms The right (panel *A*) and left (panel *B*) iliac veins are both obstructed before the iliocaval junction (arrows) the inferior vena cava does not opacify Collateral veins are present



Fig 4 Autopsy specimen Tumor thrombus (lower arrow) completely fills the opened inferior vena cava from the level of the renal veins and extends superiorly into the right atrium (upper arrow) Dark clot fills the inferior vena cava below the level of the tumor The right kidney has been resected



Fig 5 Autopsy specimen The end of the tumor thrombus (arrows) lies in the right atrial cavity It was freely mobile and was easily lifted to insert the ruler underneath

Iliac vein injections would then also be useful to resolve any doubts raised by failure to opacify the IVC from above

Tumor cells infiltrating the lumen of a large vein may initiate fibrin deposition the fibrin then serves as a framework for continued tumor growth[9] Such tumor thrombi involving the inferior vena cava are particularly likely to occur from renal and testicular cancer Ney reviewed a total of 41 cases of tumor thrombosis due to renal cancer and added 10 more in 20 of these 51 cases the tumor thrombus extended directly into the right atrium The majority of Ney s cases were hypernephromas and adenocarcinoma Recently a rare case of extension of a Wilm s tumor into the right atrium has been reported in that case echocardiographic and angiographic recordings both resembled a right atrial myxoma

We conclude that mobile right atrial masses may result from causes other than right atrial myxoma nonvisualization of the inferior vena cava may be an important clue The differentiation is important since atrial myxomas are generally resectable whereas cardiac surgery would be unwarranted in most cases of tumor thrombosis

REFERENCES

1 Prichard R. W Tumors of the heart Arch. Pathol. 51 98 19 1
2 Waxler F B Kawai N and Kasparian H Right atrial myxoma Echocardiographic phonocardiographic and hemodynamic signs, AM HEART J 83 2 1 19 2.
3. Wolfe S B Popp R L., and Feigenbaum H Diagnosis of atrial tumors by ultrasound Circulation 39 C1 1969
4 Kerber R. E Kelly D H., and Gutenkauf C H Left atrial myxoma Demonstration by stop-action cardiac ultrasonography Am J Cardiol 34 838 19 4
5 Goldschlager A., Popper R Goldschlager N Gerbode F and Prozan G Right atrial myxoma with right to left shunt and polycythemia presenting as congenital heart disease Am J Cardiol. 30 8 19 2
6 Steiner R E Radiologic a pects of cardiac tumors, Am J Cardiol 21 344 1968
7 Vidner B Atsmon A Aygen M and Levy M J Right atrial myxoma Isr J Med. Sci. 7 1106 1971
8 Glazer M., Kioschos J M Kroetz F W., Lawrence M S and Korns, M E Simulation of right atrial myxoma by metastatic leiomyosarcoma Cancer 27 2 9 19 1
9 Hanfling S M Meta tatic cancer to the heart Circulation 22 4 4 1960
10 Ney C Thrombosis of the inferior vena cava associated with malignant renal tumors J Urol. 55 583 1946
11 Farooki, Z. Q Henry J G and Green F W Echocardiographic diagnosis of right extension of Wilms tumor Am. J Cardiol. 36 363, 1975

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Clinical pathologic conference

A conversation on prosthetic valve endocarditis

Ernest N Arnett M D *
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A Julian Garvin, M D, Ph D
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DR ROBERTS The starting point for this discussion on prosthetic valve endocarditis will be a description of a patient with this fatal complication of cardiac valve replacement

DR KASTL This 47 year old man (J G #1123701) was in good health until 11 months before death when symptoms of fatigue and exertional dyspnea appeared four weeks after a dental procedure Hospitalization four months after onset of symptoms (seven months before death) revealed anemia a colonic filling defect, periodic fever and *Streptococcus bovis* in several blood cultures Penicillin 20 million units intravenously per day was administered for six weeks the fever rapidly disappeared but murmurs of mitral and aortic regurgitation and signs of congestive heart failure appeared Digoxin and diuretic therapy resulted in transient improvement of the congestive heart failure and the colonic mass which proved to be a benign polyp was resected He returned home but heart failure quickly returned and he was hospitalized now in functional Class IV (New York Heart Association classification) 55 days before death Digoxin furosemide and aldactone produced a 20 pound weight loss Subsequently at cardiac catheterization the pressures in mm Hg were pulmonary artery wedge mean 35 a wave 35 v wave 55 pulmonary artery 60/35 (mean 50), right ventricle 60/15 and right atrial mean 15 a wave 22 and v wave 17 Multiple blood cultures during that hospitalization were negative He was transferred to the National Heart Lung and Blood Institute (NHLI) 37 days before death

The blood pressure was 140/70 mm Hg cardiac rate 90 beats per minute and respiratory rate 20 breaths per minute The jugular venous pressure was elevated and the carotid upstroke was rapid but weak Basilar rales were present in both lungs The second heart sound split paradoxically and both third and fourth heart sounds were present A Grade 3/6 decrescendo diastolic murmur was present along the left sternal border and a Grade 2/6 holosystolic murmur and a Grade 2/6 middiastolic rumbling murmur were present at the apex The anteroinferior edge of the liver was palpable 4 cm below the right costal margin Chest roentgenograms (Fig 1) showed marked cardiac enlargement and electrocardio



Fig 1 Posteroanterior chest roentgenogram 4 days before valve replacement

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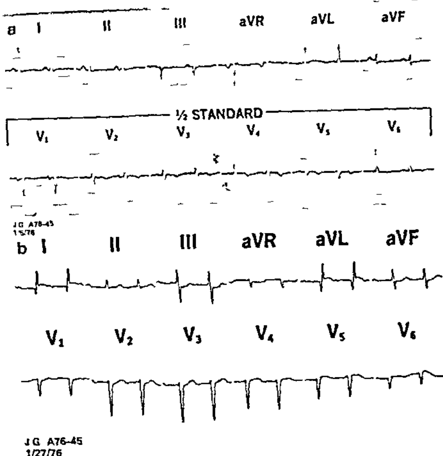


Fig 2 Electrocardiograms *a* Four days before valve replacements showing changes of left ventricular hypertrophy and left atrial enlargement *b* Eighteen days postoperatively (10 days before death) Q waves are present in Leads I aVR aVL and V₆ the R waves in the precordial leads are of markedly diminished amplitude and the ST segments are elevated in Leads I aVL and V through V₆ In addition the P R interval is prolonged

gram (Fig 2a) showed left ventricular hypertrophy The hematocrit was 37 per cent and the white blood count 11 900 per cubic millimeter Simultaneous aortic and left ventricular pressures were 120/50 and 120/30 mm Hg respectively Cineangiography revealed severe aortic and mitral valve regurgitation but good left ventricular function

The aortic valve was replaced with a No 10A model 2320 Starr Edwards prosthesis and the mitral valve with a 33 mm Hancock xenograft 28 days before death Both the excised aortic valve and the excised mitral valve (Fig 3) contained one or more perforations in the cusps Histologic examination of the excised valves revealed no evidence of active infection

During the first 24 hours postoperatively excessive bleeding necessitated repeat thoracotomy Although no specific bleeding sites were found a large quantity (2 000 ml) of blood was evacuated from the mediastinum Oxacillin 4 Gm intravenously per day and streptomycin 1 Gm intramuscularly per day were started at the time of the initial operation and continued for 10 and 7 days respectively All chest tubes were removed on the fourth postoperative day Two days later fever (38 5° C) was noted but he otherwise appeared to be doing well Nine days postoperatively ventricular fibrillation occurred but electroshock was successful in restoring sinus rhythm Electrocardiograms following this episode showed diffuse nonspecific ST segment and T wave abnormalities Over the ensuing 4 days he continued to have frequent ventricular premature beats On the 17th postoperative day his temperature rose to 39 5 C the white blood cell

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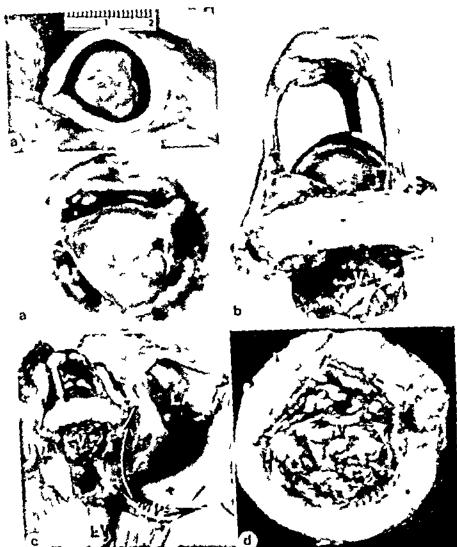


Fig 4 Infected aortic valve prosthesis *a* Prosthesis viewed from above in place and *a* after removal Thrombus covers the apex of the cage *b* Excised prosthesis viewed laterally *c* Longitudinal section showing aortic prosthesis in place The mitral valve prosthesis has been excised The aortic anulus is necrotic and so is the adjacent portion of mitral anulus. A large vegetation *(V)* is present in the primary orifice of the prosthesis its obstructive nature is better seen in *d* a view of the prosthesis from the left ventricular *(LV)* aspect *LA* = left atrium

this patient s infective endocarditis which had involved presumably both anatomically and functionally normal valves was *Streptococcus bovis* The cause of the prosthetic valve endocarditis in him however was *Staphylococcus epidermidis* Dr Arnett could you summarize the organisms found in our previous 22 patients with prosthetic valve endocarditis?

Dr Arnett Among our 22 previous necropsy patients with prosthetic valve endocarditis *Staphylococcus (epidermidis* in 10 and *aureus* in three) caused the infection in 13 (59 per cent) In the other nine patients nine different organisms caused the infection Of these later nine organisms three were Gram negative bacteria and two were fungi.

Dr Roberts We have found it useful to subdivide patients with prosthetic valve endocarditis into those with early infection i e appearing within two months of valve replacement and those with infection appearing later i e those with signs of cardiac infection appearing longer than two months after operation Dr Arnett have there been any differences in the types of infecting organisms in patients with early prosthetic valve endocarditis as contrasted to those in

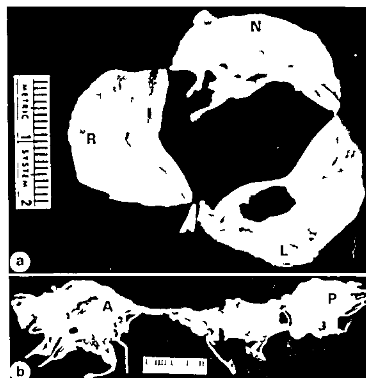


Fig 3 Operatively excised aortic *(a)* and mitral *(b)* valves A single perforation is present in the left *(L)* and right *(R)* coronary cusp and multiple ones are present in the noncoronary *(N)* cusp A perforation is present in the anterior *(A)* mitral leaflet and several chordae tendineae from the posterior *(P)* mitral leaflet are absent

count was 14 500 per cubic millimeter and blood cultures were positive for *Staphylococcus epidermidis* Oxacillin, 12 Gm intravenously per day was reinstituted The following day the blood pressure dropped to 95/70 mm Hg and the electrocardiogram (Fig 2*b*) showed changes of an acute anterolateral myocardial infarction On the nineteenth postoperative day splinter hemorrhages were noted the white blood cell count was 17 000 per cubic millimeter and blood cultures again were positive for *S epidermidis* resistant to penicillin but sensitive to both oxacillin and cephalosporin On the twenty first postoperative day he lost consciousness his temperature rose to 39° C and his systolic blood pressure fell to 90 mm Hg During insertion of a catheter into a jugular vein a collection of pus was entered and Gram stain and culture of the aspirated material disclosed *S epidermidis* Exploration of the mediastinum revealed no focal collections of pus Oxacillin was stopped and cephalosporin 12 Gm intravenously per day was started Over the next four days consciousness returned the blood pressure rose to 110/60 mm Hg but the white blood count was 27 000 per cubic millimeter and fever and positive blood cultures continued On the twenty seventh postoperative day his blood pressure suddenly dropped and he died the next day

Dr Garvin Necropsy (A76 45) disclosed no residual pus in the chest The heart weighed 660 Gm and the anterolateral left ventricular wall from midportion to apex was necrotic Large vegetations closed the primary orifice of the aortic valve prosthesis and a fibrin thrombus was present at the apex of its cage (Fig 4) Although the aortic prosthesis remained attached the site of attachment of the prosthesis was necrotic Necrosis of the valve anulus, however was apparent only after removal of the prosthesis (Fig 5) The ring infection extended through the atrial spetum into the right atrium and into the adjacent portion of the prosthetic mitral anulus Histologic sections from the site of attachment of the aortic prosthesis revealed numerous colonies of Gram positive cocci Examination of subserial sections of the extramural coronary arteries revealed total obstruction of the lumen of the left anterior descending coronary artery by a septic embolus (Fig 6) Sections of myocardium showed numerous foci of suppurating and nonsuppurating inflammation The lungs were edematous and contained foci of acute inflammation The walls of the small muscular pulmonary arteries were thick Both the liver (2 600 grams) and spleen (670 grams) were enlarged and multiple infarcts were present in the spleen Focal collections of mononuclear cells were present in the renal interstitium but otherwise the kidneys were normal

Dr Roberts The above described patient provides an opportunity to apply information previously derived from a study of 22 necropsy patients with fatal prosthetic valve endocarditis to the present patient [1] To begin this discourse Dr Arnett how do you define Prosthetic Valve Endocarditis?

Dr Arnett Prosthetic valve endocarditis is an infection involving a prosthetic cardiac valve in a patient in whom no active infective endocarditis was present at the time of prosthetic valve insertion In other words the infection was acquired after valve replacement Although the present patient s valvular disease resulted from infective endocarditis the infection was healed at the time of valve replacement

Dr Roberts Dr Kastl in your presentation of this patient you mentioned that the cause of

bypass equipment.[5,6] Dr Arnett, what have been the predisposing factors in patients with late prosthetic valve endocarditis?

Dr. Arnett: Late prosthetic valve endocarditis presumably results from transient bacteremia and the source of the bacteremia is often obscure.[3,7] Among our previous 22 necropsy patients with prosthetic valve endocarditis, 14 had the onset of symptoms of prosthetic endocarditis longer than two months after operation. Predisposing factors were apparent in only five of them: dental procedures in two, and in one patient each, skin graft infection, prolonged use of an intravenous catheter, and prolonged use of a transthoracic pacing wire.

Dr Roberts: Dr Arnett, you mentioned a similarity between early and late prosthetic endocarditis in regard to the types of infecting organisms. Are there distinct clinical differences between patients with prosthetic valve endocarditis appearing early after operation as contrasted to those with infection appearing late?

Dr Arnett: Prosthetic valve endocarditis occurring in the early postoperative period is often more difficult to diagnose. Signs of prosthetic infection may be masked by other more common postoperative complications, and transient bacteremia may be attributed to another cause. That was the situation in the present patient: persistent staphylococcal bacteremia was attributed to the known mediastinal infection and the diagnosis of prosthetic valve endocarditis was never established during life. When fever and bacteremia appear suddenly in an otherwise well patient months or years after cardiac valve replacement, however, a diagnosis of prosthetic valve endocarditis is usually made quite readily.

Dr Roberts: It is worth emphasizing, however, that the combination of fever and positive blood culture in a patient with a prosthetic cardiac valve, especially in the early postoperative period, does not always indicate the presence of prosthetic valve endocarditis. We recently studied at necropsy a patient who was diagnosed during life as having mitral prosthetic valve endocarditis on the basis of fever, cerebral episodes consistent with emboli, and a blood culture which grew *Staphylococcus epidermidis*. She received antibiotics during most of her four month postoperative period and, at necropsy, no prosthetic valve endocarditis was found. A left ventricular aneurysm, however, was present immediately

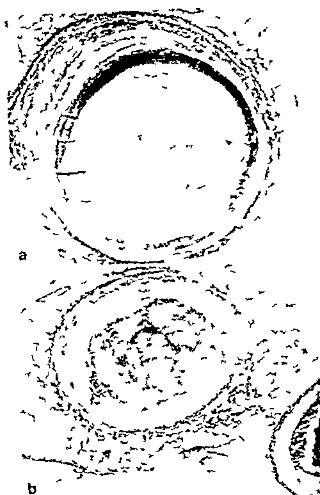


Fig 6 Left anterior descending coronary artery. *a*, Proximal 1 cm and *b*, a distal branch. The lumen is totally obstructed by a septic embolus. (*a*, Elastic van Gieson stain; *b*, hematoxylin and eosin stain; both × 12.)

caudal to the mitral anulus and a thrombus which presumably had been infected at one time was present in the aneurysm. The latter appeared to have been the source of cerebral emboli.

Although the present patient's aortic valve prosthesis was almost totally obstructed by vegetative material, a diagnosis of endocarditis was never established, presumably because signs of prosthetic dysfunction were absent. Dr Arnett, do patients with prosthetic valve endocarditis usually have signs of prosthetic dysfunction?

Dr Arnett: This patient was somewhat unusual. Infection of an aortic valve prosthesis usually results in detachment of the prosthesis, not obstruction, and signs of aortic regurgitation are usually present. Eleven of our previous 15 necropsy patients with aortic prosthetic infection had signs of aortic regurgitation and in each of them the prosthesis was at least partially



Fig 5 Ring abscess and acute myocardial infarct *a* Longitudinal section of heart showing the ring abscess involving the entire aortic anulus and the portion of mitral anulus adjacent to the aortic valve A large transmural infarct is present in the anterior wall of left ventricle (in brackets) *Ao* = aorta *LA* = left atrium *LV* = left ventricle *RV* = right ventricle *VS* = ventricular septum *b* Histologic section of the anterior left ventricular wall The myocardial cells are necrotic and numerous polymorphonuclear leukocytes are present (Hematoxylin and eosin stain × 330) *c* Opened right atrium tricuspid valve and right ventricle *(RV)* The aortic ring abscess has extended through the adjacent atrial septum and is visible in right atrium *(dashed circle)* *CS* = ostium of coronary sinus *STL* = septal tricuspid leaflet *d* Histologic section showing colonies of Gram positive cocci in the necrotic aortic valve anulus (Brown and Brenn stain × 880)

whom the infection appeared months or years after valve replacement?

Dr Arnett Among patients with early prosthetic valve endocarditis *Staphylococcus epidermidis* has been the most frequent causative organism [4] Among patients with late prosthetic valve endocarditis both staphylococci and streptococci have been frequent causes however the former have caused most cases of necropsy proven late prosthetic valve endocarditis and the latter relatively few

Dr Roberts Among patients with early prosthetic valve endocarditis it is presumed that the infection either was incurred at operation or resulted from a wound infection The former may result from contamination of cardiopulmonary

patients with natural valve endocarditis ring abscess was common only in patients with aortic valve infection Because heart block in patients with infective endocarditis is usually due to extension of ring abscess into the ventricular septum it is more frequent in patients with prosthetic endocarditis than in patients with natural valve endocarditis

The second major difference between patients with prosthetic endocarditis and those with natural valve endocarditis is the frequency of *valvular obstruction* from infective endocarditis The hemodynamic consequence of natural valve endocarditis is almost always regurgitation valvular obstruction is rare The hemodynamic consequence of prosthetic valve infection often is obstruction especially when a mitral prosthesis is infected

REFERENCES

1 Arnett E N and Roberts W C Prosthetic valve endocarditis A clinico pathologic analysis of 22 necropsy patients with comparison of observations to 74 necropsy patients with active infective endocarditis involving natural left sided cardiac valves, Am J Cardiol 38 281 1976
2. Slaughter L Morris J E and Starr A Prosthetic valvular endocarditis A 12 year review Circulation 47 1319 1973
3. Dismukes, W F Karchmer A W Buckley M J Austen W G., and Swartz M N Prosthetic valve endocarditis Analysis of 38 cases Circulation 48 365 1973
4 Wilson W R Jaumin P M Danielson G K Giuliani E R Washington J A and Geraci J F Prosthetic valve endocarditis, Ann Intern Med 82 751 1975
5 Ankeney J L and Parker R F Staphylococcal endocarditis following open heart surgery related to positive intraoperative blood cultures *in* Prosthetic heart valves, edited by Brewer L A III Springfield Ill 1969 Charles C Thomas Publisher pp 719-730
6. Blakemore W S McGarrity G J Thurer R J Wallace H W MacVaugh H., III and Conell L L. Infection by air borne bacteria with cardiopulmonary bypass, Surgery 70 830 1971
7 Kloster F E Diagnosis and management of complications of prosthetic heart valves Am J Cardiol 35 872, 1975
8. Sande M A Johnson W D Jr Hook E W., and Kaye D Sustained bacteremia in patients with prosthetic cardiac valves N Engl J Med 286 1067 1972.
9 Arnett F N and Roberts W C Valve ring abscess in active infective endocarditis. Frequency location and clues to clinical diagnosis from study of 95 necropsy patients Circulation 54 140 1976
10 Roberts W C Ewy G A Glancy D L. and Marcus F I Valvular stenosis produced by active infective endocarditis Circulation 36 449 1967
11 Arnett F N and Roberts W C Active infective endocarditis A clinico pathologic analysis of 137 necropsy patients Current Concepts in Cardiology (In press October 1976 issue)

detached Only one previous patient had aortic prosthetic obstruction from infection and he had clinical signs of aortic valve obstruction In contrast to aortic prosthetic infection, mitral infection usually causes obstruction of the prosthesis, but signs of mitral obstruction usually are not detected None of our seven patients with mitral prosthetic endocarditis had clinical signs of prosthetic dysfunction but at necropsy five of them had large vegetations obstructing the orifice of the prosthesis

DR ROBERTS This patient had infection behind the site of attachment of the prosthesis i e, in the valve ring Dr Arnett would you comment on the frequency of ring abscess among necropsy patients with prosthetic valve endocarditis?

DR ARNETT Infection behind the sewing ring or ring abscess is a consistent morphologic feature of prosthetic valve endocarditis Ring abscess was present in each of our 22 previous patients all of whom had rigid framed prosthesis In two thirds of them the entire circumference of the valve anulus was necrotic Extension of the ring infection into adjacent cardiac structures also is common especially in the patients with an infected aortic prosthesis In nine of our previous 15 patients with aortic prosthetic valve endocarditis, the ring abscess burrowed through the cardiac septum into ring atrium just as it did in the present patient

DR ROBERTS Thus ring abscess is to be expected in patients with infection involving rigid frame prostheses Indeed the infection in these patients nearly always involves the site of attachment of the prosthesis and this is why patients with prosthetic valve endocarditis are so difficult to treat If the infection was limited to the prosthesis an infected prosthesis could be excised and replaced with another prosthesis In the present patient as in most of the others the entire valve anulus was necrotic and although he had received appropriate antibiotic therapy intravenously for four weeks numerous colonies of viable appearing Gram positive cocci were present in the valve ring at necropsy This patient developed prolongation of the PR interval presumably from extension of the aortic ring abscess into the cephalad portion of the ventricular septum Dr Arnett, how common are atrioventricular conduction defects in patients with aortic prosthetic endocarditis?

DR ARNETT Among our previous 15 patients with aortic valve prosthetic endocarditis five developed complete heart block and two others developed left bundle branch block In each of these patients the ring abscess had extended into the basal portion of the ventricular septum

DR ROBERTS The present patient had multiple infarcts in the spleen as well as a transmural acute myocardial infarct Are systemic emboli common in patients with prosthetic valve endocarditis?

DR ARNETT Fourteen of our 22 previous necropsy patients (64 per cent) had gross infarcts in other organs The organs most frequently involved were spleen (12 patients) kidney (7 patients) and brain (7 patients) Only one of the previous 22 patients however, had a transmural acute myocardial infarct from a coronary arterial embolus

DR ROBERTS We have not touched on the frequency of prosthetic valve endocarditis We have examined at necropsy approximately 450 patients in whom one or more cardiac valves had been replaced by prostheses Twenty three of them (5 per cent) including the patient described herein had infection involving a prosthetic valve Thus although prosthetic valve endocarditis is a devastating complication of cardiac valve replacement fortunately it is infrequent Although its exact frequency is uncertain it may be less than 1 per cent per year among patients with prosthetic cardiac valves In the early days of cardiac valve replacement prosthetic infection in the early postoperative period was more common than in the late postoperative period Now, however it is likely that infection occurring late is more common than that occurring early simply because there are large numbers of patients with prosthetic valves

Dr Arnett and I have studied 74 patients with active infective endocarditis involving natural left sided cardiac valves Dr Arnett would you summarize the major differences between our patients with prosthetic endocarditis and those with natural valve infective endocarditis

DR ARNETT Comparison of observations in the 22 patients with prosthetic valve endocarditis to those in the 74 patients with active left sided valvular endocarditis revealed two major differences Ring abscess was present in each of the patients with prosthetic valve endocarditis regardless of the site of the prosthesis Among the

stresses from horizontal deceleration are predominately placed upon the aortic isthmus because of the differential rates of deceleration of the mobile aortic arch and the relatively fixed descending aorta whereas the stresses from crushing forces are placed upon the aortic arch and ascending aorta

Experimental studies in dogs subjected to horizontal linear impact trauma to the sternum have shown lengthening of the aorta during the impact This lengthening creates a pressure wave in the aortic blood column with a resultant waterhammer effect greatest on the ascending aorta Also experimentally it has been shown that during compression trauma to the chest the sternum is displaced almost next to the vertebral column This marked displacement of the sternum perhaps compresses the aortic arch over the spinal column and might be the possible mechanism for rupture of the aortic arch From all these forces acting upon the aorta during blunt trauma it appears that the torsion stress and the stress from waterhammer effect are greater at the aortic root and the shearing and bending stresses predominate at the isthmus

Pathophysiology and clinical manifestations Because of the frequency of other coexisting lethal injuries particularly cardiac with rupture of the ascending aorta and perhaps because there is no parietal pleura overlying this aortic segment almost all patients who survive to reach medical facilities are those with rupture of the aortic isthmus just distal to the origin of the left subclavian artery

The tear from aortic rupture is vertical to the axis of the aorta involves the intima and media and may extend partly or completely around the entire circumference of the aorta Occasionally multiple aortic tears may be found The two ends of the torn aorta may be separated for various distances up to 8 cm and the distal end may be infolded inward without dissection The expanded false aneurysm or mediastinal hematoma and the infolded distal torn end of the aorta may result in characteristic symptoms and signs which cause the diagnosis to be strongly suspected [illegible] The patient because of the expansion of the false aneurysm may complain of chest pain and particularly midscapular back pain in addition to pain in other parts of the body The expanding false aneurysm may also partially narrow the aortic lumen and even the lumen of the left subclavian artery by external compression The torn intima and media may act as a ball valve flap and this in conjunction with the expanding false aneurysm may cause partial aortic obstruction leading to the acute coarctation syndrome manifested by increased blood pressure and pulse amplitude in the upper extremities[10-12] The obstruction of the aortic lumen and/or of the intercostal arteries may be of such a severe degree as to lead to spinal cord and renal ischemia manifested by weakness of the lower extremities and/or anuria Turbulence at the region of the aortic rupture occasionally results in the development of a systolic murmur heard at the base of the heart or in the midscapular area The development of a false aneurysm at the site of aortic rupture results in a variety of findings on routine chest roentgenography including obscuration of the aortic knob and the aortic arch displacement of the trachea to the right depression of the left mainstem bronchus narrowing of the carinal angle and the most common finding of all widening of the superior mediastinum [illegible]

Because of the severe trauma to which patients with aortic rupture are usually subjected they frequently have other associated injuries including contusion of the lungs and heart fracture of the ribs sternum extremities and pelvis intra abdominal and central nervous system injuries and rupture of the diaphragm In addition to chest pain and pain in other parts of the body the patients may complain of dyspnea but these symptoms are not specific of aortic rupture

A review of the clinical manifestations of our cases however and those reported with acute rupture of the aorta has revealed the presence of a diagnostic triad of manifestations found in more than half of the cases This triad includes (1) increased blood pressure and pulse amplitude in the upper extremities (2) decreased blood pressure and pulse amplitude in the lower extremities and (3) roentgenographic evidence of widening of the superior mediastinum [illegible] Although the true incidence (9[illegible] to 100 per cent) of roentgenographic evidence of widening of the mediastinal shadow in patients with aortic rupture is quite well known since almost all treated patients with such injury have had chest roentgenography the true incidence of the changes of arterial pressure and pulse in the extremities is not clear because it seems likely that the legs are not specifically examined for pulsation particu

Great vessels injury

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Traumatic injuries of the great vessels constitute a major diagnostic and therapeutic challenge[1] They may be associated with massive hemorrhage, profound shock and other multiple organ wounds which may mask the great vessel injuries until they manifest in a catastrophic way The most common cause of trauma to the great vessels is mechanical injury produced by a physical nonpenetrating or penetrating force Other very rare causes which will not be considered in this article are those secondary to diagnostic and therapeutic procedures utilized in the management of heart and other diseases i e arteriography cardiac catheterization tracheostomy etc

Nonpenetrating trauma to the great vessels may cause (1) rupture of the aorta or (2) rupture of the great arteries whereas the penetrating trauma may produce (1) isolated penetrating wounds of the great vessels or (2) when associated with wounds of other vessels or of cardiac chambers may result in an arteriovenous or aortocardiac fistula

Rupture of the aorta

Rupture of the aorta is one of the most lethal injuries sustained from blunt trauma Vesalius in 1557 reported the first case with such injury but premortem clinical recognition of this entity did not emerge until the last 2 to 3 decades Although in the past traumatic rupture of the aorta was considered a very unusual occurrence recent reports showed that this injury occurs with alarming frequency and it has been encountered in one out of every six patients who died from blunt chest trauma secondary to an automobile accident[5-8] Therefore from the viewpoint of the practicing physician an awareness of the possible occurrence of aortic rupture in vehicular accident victims is of more than academic importance particularly since 10 to 20 per cent of the patients with rupture of the aorta survive long enough to be treated successfully if diagnosis is made and treatment instituted promptly

The overwhelming majority of the patients reported with aortic rupture are victims of vehicular accidents Other forms of crushing injuries and falls from a height have also resulted in rupture of the aorta Most of the victims with aortic rupture are young adults the largest group being between 20 and 30 years of age with males predominating in a ratio of 9 1[9] Rupture of the aorta is often overshadowed by the more overt manifestations of musculoskeletal abdominal and cerebral trauma and may manifest itself in a catastrophic manner usually in the immediate postinjury period hours later and less frequently days or weeks later Therefore an awareness of the possibility of such an injury in every patient injured by blunt trauma is a prerequisite to early diagnosis and treatment of this lethal injury

Sites and mechanism of rupture Rupture of the aorta usually occurs in the ascending aorta and in the descending aorta just distal to the origin of the left subclavian artery It has been very rarely observed in the aortic arch or the distal descending thoracic and the abdominal aorta

The rupture occurs either from direct blunt force to the chest vertical deceleration horizontal deceleration with or without chest compression or from crushing injuries involving some flexion mechanism to the spine As a result of these forces certain stresses on the aortic wall are created a shearing stress in a radial direction a bending stress in the long axis of the aorta and a torsion stress tangential to the aortic wall The

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injuries to the heart or other great vessels[1] When the intrapericardial segment of one of the great vessels is injured cardiac tamponade with or without hemothorax is commonly the presenting picture Penetrating wounds of the extrapericardial segment of the great vessels manifest with massive hemothorax with or without hemorrhagic shock when bleeding in the free pleural space occurs or with symptoms and signs of compression of the superior vena cava trachea or esophagus when large mediastinal hematoma occurs Carotid or subclavian artery injury may present with external or intrathoracic bleeding from the lower neck wound or progressively enlarging neck hematoma or an absent or weak pluse distal to the wound and the patient may be hemiplegic or comatose Patients with penetrating wound of the great arteries may immediately or later develop an arteriovenous fistula and may or may not have signs and symptoms of congestive heart failure and a systolic or continuous murmur may be heard at the wound area

Diagnosis The diagnosis of great vessel injury should be suspected in a patient with penetrating wound of the thorax neck or even upper abdomen when the above clinical manifestations are present or when there is suggestive evidence that the missile or knife has traversed the mediastinum and particularly when there is widening of the mediastinal shadow

When emergency thoractomy for bleeding is not required the suspected diagnosis of great vessel injury should be confirmed with arteriography to define the type and site of the lesion so that the proper surgical approach can be planned

Treatment The initial management of the patients with great vessel injury is dependent upon its clinical manifestations but usually involves provision of adequate ventilation restoration of circulating blood volume and relief of cardiac tamponade The expansion of the circulating volume can be effectively done if needed with the autotransfusion of the blood drained from their hemothorax When emergency thoracotomy is needed to control the intrathoracic bleeding the chest and neck should be widely prepared and draped For cases requiring emergency exploration for bleeding there is no single incision which will satisfy all the needs Therefore it is essential that the initial incision provide sufficient and quick exposure to control the bleeding whatever its site is and that it will be feasible to extend it in any direction necessary to obtain good exposure for the effective repair of the wound An anterolateral incision through the fourth intercostal space has been commonly used in our institution for exploratory thoracotomy which after bleeding is controlled with intrathoracic pressure may be extended if needed to the opposite pleural space to the neck or posteriorly to the spine Also for selected patients with intrathoracic bleeding and strong evidence that an anteriorly located great vessel is injured we have used the conventional midsternotomy incision This incision provides good exposure for the repair of wounds of all thoracic vessels except of the descending aorta or of the branches of pulmonary artery Either of these two incisions when used for the emergency repair of an undefined thoracic vascular injury may be found to have limitations For this reason when a great vessel injury is suspected arteriography should be performed whenever possible to define the site of the injury and select the best incision for its repair

The repair of the vascular injury can be performed after tangential clamping of the involved vessel when feasible or after its cross clamping with or without some form of shunt or cardiopulmonary bypass When cross clamping of the ascending aorta is required for the repair of an aortic wound or an aortocardiac or an aortopulmonary fistula total cardiopulmonary bypass should be utilized Similarly when cross clamping of the descending aorta is needed for the repair of a wound a temporary external shunt should be utilized to protect the spinal cord from ischemic injury[1,3] Repair of innominate artery wounds should be done with an internal or external temporary shunt

The results of treating patients with penetrating injuries of the great vessels are quite good Of the 36 victims treated at Grady Memorial Hospital from 1965 to 1972 29 recovered[1]

REFERENCES

1 Symbas P N Traumatic injuries of the heart and great vessels Springfield Ill. 1972 Charles C Thomas pp 149-173
2 Vesalius A *In* Bonetus T., editor Sepulchretum sive anatomia practica ex cadaveribus morbo denatis Geneva 1700 Sec 2 p 290
3 Strassman G Traumatic rupture of the aorta AM HEART J 33 508 1947

larly after the patient is brought out of shock Therefore, perhaps the incidence of the pulse and pressure changes in the extremities of patients with aortic rupture is more than likely higher than has been reported

The clinical manifestations of chronic rupture of the aorta are those of compression of structures adjacent to the aortic false aneurysm i e hoarseness dysphagia cough, even wheezing and dyspnea

Diagnosis The diagnosis of traumatic rupture of the aorta is dependent upon a high index of suspicion and an understanding of its diagnostic clues This major injury should be suspected in any patient who has sustained severe blunt trauma to the chest The diagnosis is fairly certain in a patient whose physical examination reveals the presence of the previously mentioned triad The possibility of aortic rupture is also quite strong if he has in addition to history of trauma either a *de novo* unexplained upper extremity hypertension or roentgenographic evidence of widening of the upper mediastinal shadow The diagnosis can only be established by aortography This diagnostic procedure should be performed as soon as rupture of the aorta is suspected on the basis of these signs Aortography should be performed percutaneously via the transaxillary or transfemoral route Venous aortography should be utilized only if the percutaneous transarterial one is unsuccessful Aortography will demonstrate the false aneurysm at the site of the aortic rupture and one or two linear filling defects just proximal and distal to the aneurysm Chronic rupture of the aorta should be suspected when routine chest roentgenography of a patient with a history of previous severe blunt trauma demonstrates a spherical lesion of the upper posterior mediastinum and this should again be confirmed by aortography which will demonstrate the aneurysm of the aorta

Treatment The danger of exsanguination is ever present in the patient with aortic rupture For this reason repair of the injury should be performed as soon as possible The repair should be done under some form of bypass in order to protect the spinal cord from ischemic injury Several techniques for bypass have been utilized Although in the past left atrial to femoral artery bypass was most frequently used, [1] the femoral vein to femoral artery bypass appears more practical and it has been used predominately at our institution In selected cases a temporary external shunt from ascending aorta aortic arch or subclavian artery to the descending aorta or femoral artery has also been employed for the repair of aortic rupture[15] The external shunt should be used exclusively in patients with rupture of the aorta when systemic heparinization is contraindicated particularly in patients with coexisting central nervous system injury This shunt can easily be constructed from plastic tubing connected to two arterial cannulas and it is primed with sterile 0 9 per cent saline solution

Temporary nonsurgical treatment with guanethidine and reserpine has been used in the management of patients with acute aortic rupture and it might be an excellent adjunct in the treatment of the patients in whom stabilization of other injuries or coincident infection may require some delay before repair of the rupture is carried out[1] or when surgical facilities are not available The value of this form of therapy however remains to be clarified The results of the repair of aortic rupture are most rewarding Five of the six patients with rupture of the aorta repaired shortly after their injury (during a 4 year period at our institution) completely recovered from their injuries and only one died 2 days after operation from a coexisting intracranial injury[14]

Penetrating wounds of the great vessels

The true incidence of penetrating wounds of the great vessels is not known since many of the victims of such wounds succumb shortly after the injury and autopsy examination is not done on all patients dying from chest trauma With increase in violence however and improved patient transportation and resuscitation more patients arrive alive to receive definitive treatment

A penetrating wound of the great vessels is usually the result of a bullet or knife wound to the chest or neck and rarely may be due to puncture wound from other sharp objects i e bone fragments needles pins etc The injuries may involve the ascending aorta aortic arch descending aorta and other arteries veins or the heart resulting in an arteriovenous and arteriocardiac chamber fistula

Clinical manifestations The clinical picture of penetrating wound of the great vessels is dependent upon the site and the size of the wound and the presence of other injuries including

injuries to the heart or other great vessels [1] When the intrapericardial segment of one of the great vessels is injured cardiac tamponade with or without hemothorax is commonly the presenting picture Penetrating wounds of the extrapericardial segment of the great vessels manifest with massive hemothorax with or without hemorrhagic shock when bleeding in the free pleural space occurs or with symptoms and signs of compression of the superior vena cava trachea or esophagus when large mediastinal hematoma occurs Carotid or subclavian artery injury may present with external or intrathoracic bleeding from the lower neck wound or progressively enlarging neck hematoma or an absent or weak pluse distal to the wound and the patient may be hemiplegic or comatose Patients with penetrating wound of the great arteries may immediately or later develop an arteriovenous fistula and may or may not have signs and symptoms of congestive heart failure and a systolic or continuous murmur may be heard at the wound area

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REFERENCES

1 Symbas, P N Traumatic injuries of the heart and great vessels Springfield Ill 197? Charles C Thomas pp 148-173
2 Vesalius A *In* Bonetus T., editor Sepulchretum sive anatomia practica ex cadaveribus morbo denatis Geneva 1700 Sec 2, p 290
3 Strassman G Traumatic rupture of the aorta Am Heart J 33 508 1947

4 Parmley L F Mattingly T W Manion W C and Jahnke E J Nonpenetrating traumatic injury of the aorta Circulation 17 1086 1958
5 Zeldenrust J and Aarts J H Traumatische aorto ruptuur bij verkeersongevallen Nedrl T Geneesk 106 464 1962
6 Greendyke R M Traumatic rupture of the aorta Special reference to automobile accidents J A M A 195 527 1966
7 Spencer F C Guerin P F Blake H A and Bahnson H T A report of fifteen patients with traumatic rupture of the thoracic aorta J Thorac Cardiovasc Surg 41 1 1961
8 Rittenhouse E A Dillard D H Winterscheid L C and Merendino K A Traumatic rupture of the thoracic aorta A review of the literature and a report of five cases with attention to special problems in early surgical management Ann Surg 170 87 1969
9 Jackson F R Berkas E M and Roberts V L Traumatic aortic rupture after blunt trauma Dis Chest 53 577 1968
10 Pate J W Butterick O D and Richardson R L Traumatic rupture of the thoracic aorta J A M A 203 1022 1968
11 Symbas P N Tyras D H Ware R E and Hatcher C R Jr Rupture of the aorta A diagnostic triad Ann Thorac Surg 15 405 1973
12 Malm J R and Deterling R A Jr Traumatic aneurysm of the thoracic aorta simulating coarctation A case report J Thorac Cardiovasc Surg 40 271 1960
13 Flaherty T T Wegner G P Crummy A B Francyk W P and Hipona F A Nonpenetrating injuries to the thoracic aorta Radiology 92 541 1969
14 Kirsh M M Crane J D Kahn D R Gago O Moores W Y Redman H Bookstein J J and Sloan H Roentgenographic evaluation of traumatic rupture of the aorta Surg Gynecol Obstet 131 900 1970
15 Gerbode F Braimbridge M Osborn J J Hood M and French S Traumatic thoracic aneurysms Treatment by resection and grafting with the use of an extracorporeal bypass Surgery 42 975 1957
16 Kahn D R Vathayanon S and Sloan H Resection of descending thoracic aneurysms without left heart bypass Arch Surg 97 336 1968
17 Aronstam E M Gomez A C O Connell T J Jr and Geiger J P Recent surgical and pharmacologic experience with dissecting and traumatic aneurysms J Thorac Cardiovasc Surg 59 231 1970
18 Symbas P N Tyras D H Ware R E and DiOrio D A Traumatic rupture of the aorta Ann Surg 178 6 1973
19 Symbas P N Kourias E Tyras D H and Hatcher C R Jr Penetrating wounds of great vessels Ann Surg 179 757 1974
20 Diveley W L Daniel R A Jr and Scott H W Jr Surgical management of penetrating injuries of the ascending aorta and aortic arch J Thorac Cardiovasc Surg 41 23 1961
21 McNalley M C and Sugg W L Traumatic communication between the aorta right atrium and left atrium A case report J Thorac Cardiovasc Surg 54 150 1967
22 Meredith J H and Bradshaw H H Fistula between aorta and superior vena cava Report of a traumatic case with surgical repair J Thorac Surg 34 278 1957
23 Morris G C Jr Foster R P Dunn J R and Cooley D A Traumatic aortico ventricular fistula Report of two cases successfully repaired Am Surg 24 883 1958
24 Norman J C Weber W J Wilson W S and Sloan H Post traumatic fistula of the aorta pulmonary artery and right ventricle Ann Surg 161 357 1965
25 Sealy W C and Fawcett B Arteriovenous fistula ascending aorta and left innominate vein A report of a case with successful surgical repair Ann Surg 142 30? 1955
26 Symbas P N and Sehdeva J S Penetrating wounds of the thoracic aorta Ann Surg 171 441 1970
27 Tarlov E and Greenfield L J Post traumatic aortic arch aneurysm with arteriovenous fistula to the innominate vein J Thorac Cardiovasc Surg 55 134 1968
28 Symbas P N Levin J M Ferrier F L Mu e A D and Sybers R G Autotransfusion and its effects upon the blood components and the recipient in Zuidema G D and Skinner D B (editors) Current topics in surgical research New York 1969 Academic Press Inc p 387
29 Symbas P N Autotransfusion from hemothorax Experimental and clinical studies J Trauma 12 689 19?
30 Adams H D and Van Geertruyden H H Neurologic complications of aortic surgery Ann Surg 144 574 1956
31 Eiseman B and Summer W B Factors affecting spinal cord ischemia during aortic occlusion Surgery 38 1063 1955

Cardiac pacing and pacemakers I Indications for pacing bradyarrhythmias

Seymour Furman M D

Bronx N Y

A wide variety of cardiac arrhythmias has become permanently controllable by electrical cardiac stimulation since Zoll s initial treatment of complete heart block with an external transcutaneous pacemaker in 1952 later wired transthoracic pacing[2] external transvenous[3] and finally implantable transvenous and transthoracic pacing Though our incomplete understanding of the nature of heart block tended to raise the question of the fixed or intermittent nature of heart block the development of non competitive (demand standby ventricular inhibited and ventricular synchronous) pacemakers about 1965 resolved the problem by enabling the implant of devices which would be capable of allowing sinus rhythm to exist and to stimulate the heart whenever the cardiac rate fell below a predetermined interval between QRS complexes

By 1965 to 1967 the basis of modern cardiac pacing for bradyarrhythmias had been established The three factors were (1) the development of an implantable device (2) the transvenous approach and (3) the ability of the pacemaker to sense cardiac activity and respond to the cardiac chamber being stimulated

The future of pacing for cardiac arrhythmias other than heart block could have been foretold by the initial clinical description of transvenous pacing in which the patient with bradycardia asystole and recurrent Adams Stokes seizures did not have classic complete heart block but rheumatic heart disease mitral valvular disease and chronic atrial fibrillation with a markedly reduced ventricular rate The immediate cause of asystole was hypopotassemia unrecognized in significance at that time but later found to be a profound causative agent for ventricular bradycardia and interruption of A V conduction

From the preliminary treatment of heart block a far wider group of arrhythmias has been treated In 1975 at Montefiore Hospital and Medical Center a total of 200 initial pacemaker implants were performed Of these 36 5 per cent were for sinus node dysfunction with brady–tachy syndrome sinus arrest or sinus bradycardia Eighteen per cent were for complete heart block and 35 per cent for intermittent or partial heart block the balance for a variety of ventricular arrhythmias and reentry tachycardias drug induced bradycardia etc Fixed complete heart block the classic arrhythmia accounted for less than 20 per cent of all arrhythmias (Table I)

The patients are a diverse group over half with arteriosclerotic heart disease one fifth with hypertension and one tenth with diabetes mellitus Rheumatic heart disease or an acute myocardial infarction as the immediate cause for the heart block accounted for another 10 per cent and 1 per cent of patients required pacing as a complication of cardiac surgery at the time of implant or at some later time in at least one case two years later (Table II)

Until about 1970 most physicians and surgeons would have considered carefully whether to implant a pacemaker in the absence of demonstrated Adams Stokes seizures Gradually a variety of minor neurologic lapses and prophylactic indications have become dominant For purposes of clarity and utility in comprehending Adams Stokes seizures they should be thought of

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4 Parmley L F Mattingly T W Manion W C and Jahnke E J Nonpenetrating traumatic injury of the aorta Circulation **17** 1086 1958
5 Zeldenrust J and Aarts J H Traumatische aorto ruptuur bij verkeersongevallen Nedrl T Geneesk **106** 464 1962
6 Greendyke R M Traumatic rupture of the aorta Special reference to automobile accidents J A M A **195** 527 1966
7 Spencer F C Guerin P F Blake H A and Bahnson H T A report of fifteen patients with traumatic rupture of the thoracic aorta J Thorac Cardiovasc Surg **41** 1 1961
8 Rittenhouse E A Dillard D H Winterscheid L C and Merendino K A Traumatic rupture of the thoracic aorta A review of the literature and a report of five cases with attention to special problems in early surgical management Ann Surg **170** 87 1969
9 Jackson F R Berkas E M and Roberts V L Traumatic aortic rupture after blunt trauma Dis Chest **53** 577 1968
10 *Pate J W Butterick O D and Richardson R L* Traumatic rupture of the thoracic aorta J A M A **203** 1022 1968
11 Symbas P N Tyras D H Ware R E and Hatcher C R Jr Rupture of the aorta A diagnostic triad Ann Thorac Surg **15** 405 1973
12 Malm J R and Deterling R A Jr Traumatic aneursym of the thoracic aorta simulating coarctation A case report J Thorac Cardiovasc Surg **40** 271 1960
13 Flaherty T T Wegner G P Crummy A B Francyk W P and Hipona F A Nonpenetrating injuries to the thoracic aorta Radiology **92** 541 1969
14 Kirsh M M Crane J D Kahn D R Gago O Moores W Y Redman H Bookstein J J and Sloan H Roentgenographic evaluation of traumatic rupture of the aorta Surg Gynecol Obstet **131** 900 1970
15 Gerbode F Braimbridge M Osborn J J Hood M and French S Traumatic thoracic aneurysms Treatment by resection and grafting with the use of an extracorporeal bypass Surgery **42** 975 1957
16 Kahn D R Vathayanon S and Sloan H Resection of descending thoracic aneurysms without left heart bypass Arch Surg **97** 336 1968
17 Aronstam E M Gomez A C O Connell T J Jr and Geiger J P Recent surgical and pharmacologic experience with dissecting and traumatic aneurysms J Thorac Cardiovasc Surg **59** 231 1970
18 Symbas P N Tyras D H Ware R E and DiOrio D A Traumatic rupture of the aorta Ann Surg **178** 6 1973
19 Symbas P N Kourias E Tyras D H and Hatcher C R Jr Penetrating wounds of great vessels Ann Surg **179** 757 1974
20 Diveley W L Daniel R A Jr and Scott H W Jr Surgical management of penetrating injuries of the ascending aorta and aortic arch J Thorac Cardiovasc Surg **41** 23 1961
21 McNalley M C and Sugg W L Traumatic communication between the aorta right atrium and left atrium A case report J Thorac Cardiovasc Surg **54** 150 1967
22 Meredith J H and Bradshaw H H Fistula between aorta and superior vena cava Report of a traumatic case with surgical repair J Thorac Surg **34** 278 1957
23 Morris G C Jr Foster R P Dunn J R and Cooley D A Traumatic aortico ventricular fistula Report of two cases successfully repaired Am Surg **24** 883 1958
24 Norman J C Weber W J Wilson W S and Sloan H Post traumatic fistula of the aorta pulmonary *artery and right ventricle Ann Surg* **161** 357 1965
25 Sealy W C and Fawcett B Arteriovenous fistula ascending aorta and left innominate vein A report of a case with successful surgical repair Ann Surg **142** 309 1955
26 Symbas P N and Sehdeva J S Penetrating wounds of the thoracic aorta Ann Surg **171** 441 1970
27 Tarlov E and Greenfield L J Post traumatic aortic arch aneurysm with arteriovenous fistula to the innominate vein J Thorac Cardiovasc Surg **55** 134 1968
28 Symbas P N Levin J M Ferrier F L Muse A D and Sybers R G Autotransfusion and its effects upon the blood components and the recipient *in* Zuidema G D and Skinner D B (editors) Current topics in surgical research New York 1969 Academic Press, Inc., p 387
29 Symbas P N Autotransfusion from hemothorax *Experimental and clinical studies J Trauma* **12** 689 1972
30 *Adams H D and Van Geertruyden H H Neurologic* complications of aortic surgery Ann Surg **144** 574 1956
31 Eiseman B and Summer W B Factors affecting spinal cord ischemia during aortic occlusion Surgery **38** 1063 1955

required to resolve the uncertainties of control of the sick sinus syndrome or to resolve the problem of whether increase in a sinus bradycardia rate from 40 per minute to 60 to 70 per minute changes a patient s mentation cardiac compensation or feeling of well being Often only such an approach with assessment by colleagues the patient and family will enable a decision to be made

Sick sinus syndrome

Subgroups of what would now be called the sick sinus syndrome have been described for many years In 1909 Laslett described a woman of 40 years of age who had syncopal attacks associated with prolonged arrest of the whole heart and distinguished by a slow irregular pulse 32 to 40 per minute punctuated by pauses to 2 to 5 seconds in duration and on jugular pulse tracing demonstrated that the auricles as well as the ventricles participate in the stop and that The condition is therefore quite different from what is known as heart block Later a patient was reported with Adams Stokes seizures because of A V block with P waves and absent ventricular response and on other occasions sinus arrest without the escape of a lower pacemaker This case too foretold the combination of A V block and sick sinus syndrome In 1954 Short reported on four patients with syncope who alternated between sinus bradycardia and auricular tachycardia The sinus rate lay between 30 to 50 per minute and during the auricular phase the ventricular rate sometimes reached 200 per minute

In 1968 Ferrer named the three varieties of the condition of sinus node dysfunction the Sick Sinus Syndrome" and recognized that there were major components (1) severe bradycardia often persistent but sometimes episodic (2) sinus arrest for brief or prolonged periods with or without replacement by an A V junctional rhythm (3) SA block not related to drug therapy (4) episodic atrial fibrillation flutter or paroxysmal atrial tachycardia alternating with a normal sinus rate or sinus bradycardia and (5) the slow recovery of sinus function after cardioversion In addition during sinus arrest or severe bradycardia symptoms are based on the absence of a satisfactory junctional escape so that disease of the AV node as well as of the conduction system is present

Those with sick sinus syndrome are of the same age group as those with heart block and indeed the two conditions co exist in about 60 per cent[21] A single group of patients deserve special mention These are young men well below the age of 50 without known associated disease of any sort who with only sinus arrest and syncope and without tachycardia have suffered major syncopal episodes and required therapy Six such patients have been treated at Montefiore Hospital and Medical Center all have remained vigorous and well after pacing Two are in their early twenties two in the mid thirties and one aged forty but who had had recurrent dizziness and syncope since age 15 and another implanted at age 45 but who had been symptomatic since age 35

The pharmacologic treatment of sinus arrest and syncope has been unsatisfactory from the first descriptions with response to parenteral atropine but without significant response to oral atropine The experience with sympathomimetics is that they increase the rate of a bradycardia but frequently produce a tachycardia Procainamide and propranolol may increase the episodes of sinus arrest and syncope Many patients with sick sinus syndrome have congestive heart failure and require digitalis and/or diuretics The digitalis is helpful in reducing the tachycardia and treating the congestive heart failure but may depress the cardiac rate

In light of the ineffectiveness of pharmacologic therapy pacing the atrium or the ventricle has been widely used Atrial pacing may be considered a logical approach and indeed has been successful but because of the incidence of associated A V conduction disease and the possibility of late development of A V block and the ineffectiveness of normal rate atrial pacing in the presence of atrial fibrillation or flutter atrial pacing is not usually used Ventricular pacing is apparently equally effective The technical difficulties associated with atrial pacing the frequent poor amplitude or the P wave for adequate pacemaker recycle and the high rate of difficulty with all atrial pacing approaches make that route less desirable

Despite the effectiveness of arrhythmia control by atrial or the more common ventricular pacing three disturbing features exist The first is the frequency with which neurologic symptoms

Table I Pacer implants (1975) Rhythm disturbance

Sinus node dysfunction	36.5%
Brady tachy syndrome	20.2
Sinus arrest	11.3%
Sinus bradycardia	5.0%
Atrial fibrillation with ventricular rate below 50	4.2%
Complete heart block	17.9%
Acquired	16.7
Congenital	1.2%
Intermittent heart block	3.1%
Wolff Parkinson White syndrome	1.2%
Other ventricular arrhythmia	2.4%
Drug induced bradycardia	1.2%
Malfunction of implanted pacer	1.2%

Table II Pacer implants (1975) Concomitant factors

Arteriosclerotic cardiovascular disease	57.4%
Hypertension	19.7%
Diabetes mellitus	9.6%
Rheumatic heart disease	4.2%
Congenital heart disease	3.2
Postcardiac surgery (recent)	0.5%
Postcardiac surgery (old)	0.5%
Acute myocardial infarct (recent)	5.3%

as the result of all cardiac conditions which produce episodic cerebral ischemia due to diminution of output of the left ventricle [1] and as every disturbance of the action of heart that begins and ends abruptly and causes such interruption of the circulation that more or less complete cerebral ischemia results [11] Symptoms may include dizziness lightheadedness brief lapses of consciousness and fainting with or without convulsions—all based on interruption of cardiac output These definitions are useful as they direct modern therapy to the circulatory arrest and its consequence with only secondary attention to the underlying cardiac rhythm [2]

Those definitions as early as 1940 remained especially pertinent as they broaden the useful definition away from complete loss of consciousness, with or without convulsions and take it to a group of lesser but troublesome neurologic manifestations Frequently the determination of whether a patient has had an Adams Stokes seizure especially where it entails lesser neurologic manifestations can be most difficult

The diagnosis of acquired intermittent or partial complete heart block, 2 1 or Mobitz II block can be made electrocardiographically [13] Once made there are few who would dispute the need for cardiac pacing Unfortunately, capture of the moment of A V dissociation may not be easy and a careful neurologic evaluation may still be required The presence of bifascicular block while strongly suggestive of a cardiac basis for accompanying syncope does not preclude the possibility of neurologic disease The problem becomes even more complex when dealing with bradycardias unrelated to heart block For example how often does *atrial fibrillation* with a ventricular rate below 50 in a patient 70 years of age or older cause symptoms of any sort and in the specific instance, is pacing required to prevent *further bradycardia? The answer is probably that* the relatively asymptomatic patient with that complex should be paced and medications such as digitalis and diuretics should be continued as needed

How slow a bradycardia is pathologic in an elderly person with a sinus mechanism and A V conduction? How slow is sinus bradycardia that requires treatment and what complex of symptoms should be considered as indicating the need for pacing? Clearly elderly patients can tolerate as benign a sinus rate of 40 to 50 per minute apparently without deleterious effect An asymptomatic sinus rate of 40 per minute or above in the older patient argues against pacemaker implant But if so what duration of sinus arrest and asystole becomes pathologic? We would probably all agree that a sinus arrest of 3.0 seconds demands treatment but does an episode of 1.5 to 1.8 seconds during an otherwise more rapid rate and without symptoms *require* pacing?

The decision concerning pacemaker implantation is often difficult and careful evaluation is required Holter monitoring carried *out around* the clock observation with continuous monitoring in the coronary care unit and provocative tests such as bundle of His studies and sinus node recovery time [1] *after rapid atrial pacing* and programmed cardiac stimulation may be required Even with all of these techniques a definitive answer concerning whether to pace or *not to* pace *may not be available If necessary* temporary cardiac pacing [16] under observation may be

node only If that cannot be demonstrated perhaps by His bundle conduction study the combination must be considered trifascicular block and an indication for pacing [49]

The following electrocardiographic patterns can be considered bifascicular block and potentially trifascicular block which will be associated with brief or prolonged complete heart block and asystole or ventricular tachycardia and/or fibrillation

1 Right bundle branch block with left axis deviation (caused by left anterior hemiblock)

2 Right bundle branch block with right axis deviation (caused by left posterior hemiblock)

3 Right bundle branch with first degree A V block (the entire left bundle must be compromised) unless it can be demonstrated that the conduction delay is in the A V node

4 Complete left bundle branch block is in itself ominous but when associated with first degree A V block the right bundle branch must also be compromised

5 Alternating bilateral bundle branch block The three fascicles are alternately blocked even during 1 1 A V conduction

Acquired complete heart block is accepted as a reason for cardiac pacing temporary or permanent as a function of the patient s outlook for survival

Congenital heart block as an isolated lesion also requires pacing if the patient is at all symptomatic or if the duration of the QRS complex is beyond 0 12 second A number of children have apparently survived to adult life [5] and such survival is an excellent portent for their future

However it is in infancy that most deaths occur and detection of complete heart block after early childhood has not taken into account those who have died As the patient with congenital heart block may be asymptomatic the needed electrocardiographic diagnosis may not be made If symptoms cause an ECG to be performed and the diagnosis is made the patient can be watched for the development of congestive heart failure bradycardia or syncope Even with adequate follow up sudden death may be the first clinical manifestation

Atrial fibrillation or flutter with ventricular bradycardia may occur because of complete heart block irrespective of the atrial arrhythmia or because of multiple concealed conduction at the A V junction

Pacing in special circumstances

Postcardiac surgery Sinus bradycardia and a variety of atrial or ventricular arrhythmias occur frequently following open heart surgery and fleeting or even permanent complete heart block occurs following complex intracardiac repair and especially that of the tricuspid valve in Ebstein s malformation [50] Even in the absence of such arrhythmias a sinus bradycardia relative to postoperative requirement frequently exists [51] As the cardiac output is markedly rate dependent postoperatively rate control by atrial or if necessary ventricular pacing is indicated Temporary myocardial wires in the atrium and ventricles which can be extracted postoperatively should be left routinely Should the patient have an indication for permanent postoperative pacing or develop one intraoperatively a permanent left ventricular myocardial lead should be left and attached to a non invasively rate variable pulse generator [5] Rate can be controlled by the implanted unit If a single rate unit is implanted the temporary leads should be used as well and rates above that of the implant will inhibit it If permanent pacemaker implant is considered a permanent left ventricular electrode can be left in place and insulated in the subcutaneous tissue Should permanent pacing be required it can be established by connecting a generator to that electrode

Acute myocardial infarction Indications for pacing in acute myocardial infarction have undergone profound change from recommendation that many patients should be paced to a therapeutic nihilism which held that mortality rates are unchanged with or without pacing The recognition that prognosis of block varies whether the infarct is anterior or inferior has caused a reassessment of the indications Anterior infarction with complete heart block implies massive myocardial damage and cardiogenic shock and/or congestive heart failure cause death in over 50 per cent of patients [5] For the inferior infarct the collected mortality rate is about 25 to 40 per cent In the former death may occur despite successful pacing in the latter survival is usual without need for pacing Nevertheless some patients persist in heart block survive and

indistinguishable for those which originally indicated pacemaker implant, persist In at least one report, 14 of 39 patients *persisted in significant* symptomatology Patients with pacemakers also have had a *high incidence of peripheral embolization,* perhaps from poor atrial *function and* formation of mural thrombi and possibly with embolization during a change in atrial *rhythm* Twenty *four per cent of one series* 10 per cent of *another,* and 13 per cent in a third suffered *such embolization* The third complication is a *death rate about twice as high* during the first year *after* implantation than those with heart block One third died during the first post implant year though in other series the first year mortality rate is about 15 per cent a figure more nearly compatible with usual heart block pacer implants Though it is suggested that mortality may be higher for this condition review of 352 patients reported and treated with cardiac pacemakers shows a mortality rate of 33 per cent over an average follow up of 24 to 30 months a figure compatible with that of the general paced population

Disturbances of A V conduction

During complete heart block cardiac function is markedly reduced in the following ways

1 The ventricular rate is slow usually between 30 to 40 beats per minute with episodes of even slower rates or arrest

2 The cardiac output is reduced and is maintained by maximum stroke volume so that increases in requirement cannot be met either by increases in rate or stroke volume

3 The arteriovenous oxygen difference is increased

4 Right ventricular and pulmonary artery systolic pressures are evaluated and congestive heart failure is common

5 Left ventricular and systemic arterial pressure systolic and to a less extent diastolic pressures are increased

6 A V dissociation and asynchrony (uncorrected even during ventricular pacing) is associated with a cyclical reduction of systemic and pulmonary pressures *and outputs* as the atrial activity moves toward and away from a physiologic sequence

Electrophysiologic defects caused by slow cardiac rates are

1 All lower pacemakers than the SA node tend to be both *slower* and less reliable Acquired complete heart block with a consistent His *bundle rhythm* and a narrow QRS complex is *commonly associated with Adams Stokes* seizures Idioventricular pacemakers are even less reliable

2 Slow cardiac rates allow the development of ectopic ventricular rhythms in single and multifocal formats and even allow the fall of premature ventricular contractions during the ventricular vulnerable period and the development of ventricular tachycardia and fibrillation as an additional rhythm to an idioventricular bradycardia [18]

Ventricular pacing ameliorates all functional disturbances except the A V dissociation and corrects the electrophysiologic disturbances In a patient with A V dissociation and a bizarre multifocal idioventricular rhythm the application of physiologic rate ventricular pacing is an immediate and effective therapy, far more so than any combination of drugs [19]

Pacing is also indicated in lesser degrees of fixed A V block because of the possibility of intermittent complete heart block with asystole, and/or ventricular tachycardia and fibrillation and syncope or sudden death Because of the possibility of intermittent complete heart block in a symptomatic patient with normal sinus rhythm during evaluation the diagnostic pattern of fascicular block is important

As there are three fascicles below *the bundle of* His the right bundle left bundle and its two subdivisions the anterior and posterior any combination of two or more may be in fixed or intermittent block Right bundle branch block or left anterior or posterior hemiblock with a normal P R interval is diagnostic of monofascicular block *and need not be considered* for pacing unless evidence for additional block or suggestive symptomatology such as syncope exists Bifascicular block with right bundle branch block with left anterior[11] or left posterior hemiblock (especially the latter) is much more ominous and if associated with syncope the burden of proof rests on the denial of cardiac origin for syncope A prolonged PR interval as well i e, bifascicular block with first degree heart block is strongly suggestive of block in the third fascicle unless it can be demonstrated that *the delay* is in the AV

9. Furman S and Schwedel J B An intracardiac pacemaker for Stokes Adams seizures N Engl J Med 261 943 1959
10. Fishberg A M Heart failure Philadelphia 1940 Lea & Febiger p 90
11. DeBoer S On the origin and essence of the Morgagni Adam Stokes syndrome Ann Intern Med 37 4? 19?
12. Stephenson H E Jr Reid L C and Hinton J W Some common denominators in 1 00 cases of cardiac arrest Ann Surg 137 731 1953
13. Donoso E Adler L N and Friedberg C K Unusual forms of second degree atrio ventricular block including Mobitz Type II block associated with the Morgagni Adams Stokes syndrome AM HEART J 67 150 1964
14. Narula O S Cohen L S Samet P Lister J W Scherlag B J and Hildner F J Localization of A V conduction defects in man by recording of the His bundle electrogram Am J Cardiol 25 ??8 19 0
15. Strauss H C Bigger J T Jr Saroff A L and Giardina E G V Electrophysiologic evaluation of sinus node functi n in patients with sinus node dysfunction Circulation 53 63 1976
16. Javier R P Maramba L C Hildner F J Cohen L S Korn M K Schoenfeld C D and Sam t P Temporary cardiac pacing Techniques and indications Chest 59 498 1971
17. Laslett E E Syncopal attacks associated with prolo ged arrest of th whole heart Q J Med 2 347 1909
18. Tuna N and Scott J W Stokes Adams attacks with imultaneous auricular and ventricular standstill Circulation 9 853 19 4
19. Short D S The syndrome of alternating bradycardia and tachycardia Br Heart J 16 208 1954
20. Ferrer M I The sick sinus syndrome in atrial disease J A M A 206 645 1968
21. Narula O S Atrioventricular conduction defects in patients with sinus bradycardia Circulation 44 1096 1971
22. Rosen K M Loeb H S Sinno M Z Rahimtoola S H and Gunnar R M Cardiac conduction in patients with symptomatic inus node disease Circulation 43 836 19 1
23. Rubenstein J J Schulman C L Yurchak P M and DeSanctis R W Clinical spectrum of the sick inus syndrome Circulation 46 5 1972
24. Conde C A Leppo J Lipski J Stimmel B Litwak R Donoso E and Dack S Effectiveness of pacemaker treatment in the bradycardia tachycardia syndrome Am J Cardiol 32 09 19 3
25. Witte V J Schroder G Dressler L and Parsi R A Die gestorte sinusknotenfunktion— sick sinus syndrom Dtsch Gesund Wes 30 350 19 5
26. Kramer D H and Moss A J Permanent pervenous atrial pacing from the coronary vein Circulation 42 4? 19 0
27. Wohl A J Laborde J Atkins J M Blomqvist C G and Mullin C B Prognosis of patients permanently paced for sick sinus syndrome Arch Intern Med 136 406 19 6
28. Aroesty J M Cohen S I and Morkin E Bradycardia tachycardia syndrome results in twenty eight pat ents treated by c mbined pharmacologic therapy and pa emaker implantation Chest 66 257 19 4
29. Fairfax A J Lambert C D and Leatham A Systemic embolism in chronic sinoatrial disorder N Engl J Med 295 190 19 6
30. Krishnaswami V and Geraci A R Permanent pacin in disorders of sinus node function AM HEART J 89 5 9 1975
31. Furman S The present status of cardiac pacing Surg Gynecol Obstet 143 645 1976
32. Sta k M F Rader B Sobol B J Farber S J and Eichna L W Cardiovascular hemodynamic functions in complete heart block and the effect of isopropylnorepinephrine Circulation 17 26 1958
33. Levinson D C Gunther L Meehan J P Jr Griffith G C and Spritzler R J Hemodynamic studies in five patients with heart block and slow ventricular rates Circulation 12 739 195
34. Samet P Jacobs W Bernstein W H and Shane R Hemodynamic sequelae of idioventricular pacemaking in complete heart block Am J Cardiol 11 591 1963
35. Brockman S K Cardiodynamics of complete heart block Am J Cardiol 16 72 1965
36. Levinson D C Shubin H Gunther L and Meehan J P Hemodynamic findings in heart block with slow ventricular rates Am J Cardiol 4 440 1959
37. Parkinson J Papp C and Evans W The electrocardiogram of the Stokes Adams attack Br Heart J 3 171 1941
38. Dressler W Observations in patients with implanted pacemaker III Frequency of ventricular tachycardia as cause of Adams-Stokes attacks and rate of pacing required for its prevention AM HEART J 68 19 1964
39. Sowton E Leatham A and Carson P The suppression of arrhythmias by artificial pacemaking Lancet 2 1098 1964
40. Narula O S and Samet P Wenckebach and Mobitz Type II A V block due to block within the His bundle and bundle branches Circulation 41 94 19 0
41. Haft J I and Lasser R P ECG patterns useful in the diagnosis of intermittent heart block J A M A 222 184 1972
42. Steiner C Lau S H Stein E Wit A L Weiss M B Damato A N Haft J I Weinstock M and Gupta P Electrophysiologic documentation of trifascicular block as the common cause of complete heart block Am J Cardiol 28 436 1971
43. Rosenbaum M B Elizari M V Lazzari J O Nau G J Levi R J and Halpern M S Intraventricular trifascicular blocks. Review of the literature and classification AM HEART J 78 450 1969
44. Nakamura F F and Nadas A S Complete heart block in infants and children N Engl J Med 270 1261 1964
45. Campbell M and Emanuel R Six cases of congenital complete heart block followed for 34-40 years Br Heart J 29 57 1967
46. Campbell M and Thorne M G Congenital heart block Br Heart J 18 90 1956
47. Michaelsson J and Engle M A Congenital complete heart block an international study of the natural history Cardiovasc Clin 4 85 1973
48. Pahlajani D B Miller R A and Serratto M Patterns of atrioventricular conduction in children AM HEART J 90 165 1975
49. Moltham M E Miller R M Hastreiter A R and Paul M H Congenital heart block with fatal Adams Stokes attacks in childhood Pediatrics 30 32 1962
50. Reemtsma K Delgado J P and Creech O Heart block following intracardiac surgery localization of conduction tissue injury J Thorac Cardiovasc Surg 39 688 1960
51. Friesen W G Woodson R D Ames A W Herr R H Starr A and Kassebaum D G A hemodynamic comparison of atrial and ventricular pacing in post

depend on permanent pacing for prolonged survival Aside from the development of second or third degree A V block those with acute myocardial infarction develop bradyarrhythmias, sinus bradycardia S A block in 5 20 per cent,[6 61] and tachyarrhythmia in about one quarter of patients[64 6] *Both can be managed with pacing* and/or medications as necessary and frequently better in a combination of both

The indications for pacing during acute *myocardial infarction at present are*

1 Symptomatic bradycardias including sinus bradycardia S A block and sick sinus syndrome

2 Drug resistant tachyarrhythmias

3 Acute onset of right or left bundle or bifascicular block

4 Acute onset of Mobitz II or complete A V block with anterior infarction

5 Rhythms probably not requiring pacing are Mobitz I (Wenckebach) block or complete A V block during inferior infarction and a rate of 40 to 50 or above without periods of greater bradycardia asystole or escape ventricular premature contractions which are readily controlled with drugs

Of perhaps greater importance is the prognosis of the patient who develops new bundle branch block during the course of acute myocardial infarction but never develops second degree or third degree A V block Such a patient is likely to go unpaced but early post recovery mortality may be high Those with new right bundle branch block and left axis deviation or right axis deviation i e left anterior or posterior hemiblock, carry an especially high mortality rate with 25 per cent of such patients dying suddenly during the first post infarction year The prophylactic management of such patients is still in dispute, most likely because neither the techniques for detecting the severity of the persistent block nor those provocative tests now available have adequate diagnostic specificity Newly developed approaches to bundle of His recording with the electrode for temporary pacing during its removal pull out His recording have already begun to add to that specificity Over 80 per cent of patients can have a simple His potential recording performed during removal of a conventional temporary pacing electrode In these patients ominous findings such as a split His potential[69] or markedly prolonged H V time alone or during lidocaine administration have distinct prognostic value[70] Further, symptomatic unpaced post infarct patients with H V time longer than 65 msec but no other evidence of heart block have a mortality rate of 69 per cent compared to 20 per cent for similar patients subjected to permanent pacing [7] Such specificity may well reduce the total number of patients who, having seemingly recovered from acute myocardial infarction, die suddenly

Finally a cautionary word concerning temporary pacing during acute myocardial infarction Those with ischemic heart disease and acute myocardial infarction are maximally sensitive to ventricular fibrillation[7] and especially to the anodal stimulus from the almost universally used bipolar temporary electrode falling in the vulnerable period of the cardiac cycle [7] Loss of pacer sensing because of decrease in QRS amplitude can be as high as 15 per cent [4] during acute infarction Under those circumstances pacer stimuli may become competitive and 14 of the 30 reported and documented cases of pacemaker caused ventricular fibrillation have been from a competitive pacer during acute myocardial infarction so that caution must be exercised pacer function must be frequently assessed and the use of the unipolar cathodal stimulation with the anode out of the ventricle must be considered

REFERENCES

1 Zoll P M Resuscitation of the heart in ventricular standstill by external electrical stimulation N Engl J Med **247** 768 1952

2 Weirich W L Gott V L and Lillehei C W The treatment of complete heart block by the combined use of a myocardial electrode and an artificial pacemaker Surg Forum **8** 360 1957

3 Lagergren H and Johansson L Intracardiac stimulation for complete heart block Acta Chir Scand **125** 562 1963

4 Chardack W M Gage A A Federico A J Schimert G and Greatbatch W Five years clinical experience with an implanted pacemaker an appraisal Surgery **58** 915 1965

5 Chardack W Gage A A and Greatbatch W A transistorized self contained implantable pacemaker for the long term correction of complete heart block Surgery **48** 643 1960

6 Friedberg C K Donoso F and Stein W G Nonsurgical acquired heart block Ann N Y Acad Sci **111** 835 1964

7 Lemberg L Castellanos A and Berkovits B Pacing on demand in A V block J A M A **191** 12 1965

8 Parsonnet V Zucker I R Gilbert L and Myers G H Clinical use of an implantable standby pacemaker J A M A **196** 784 1966

Salt intake and the treatment of hypertension*

Sodium restriction for the treatment of hypertension was recommended by Ambard and Beaujard and by Allen and Sherrill. The introduction of the rice fruit diet in the 1940's by Kempner constitutes a rediscovery of the value of sodium restriction. However, several papers inspired by his work, while documenting the central role of sodium in the blood pressure lowering effect of the rice diet, left the impression that though sodium restriction was the critical part of the rice diet for blood pressure lowering, sodium intake must be restricted to less than 400 mgm daily for any beneficial results.

The introduction of thiazid diuretics appeared to remove the necessity for sodium restriction. Current texts state and a recent article and editorial reiterate that sodium restriction is not needed in the routine treatment of hypertensive patients.

It has been shown that sheep, cattle, and other herbivores rapidly replace their sodium stores following salt deprivation. Rats placed on low sodium diets drink saline in preference to distilled water when allowed free choice. It seems likely that man might respond similarly when sodium depleted.

We have made two observations that, when taken together, suggest to us that the hypertensive patients treated with diuretics increase their Na intake enough to partially negate the antihypertensive effect of the diuretic, and that this change in behavior is associated and perhaps due to a change in salt taste threshold.

Our initial observations were made during a study where we were examining the relation between electrolyte excretion and blood pressure level. By systematic sampling after random starts we recruited forty clusters of five black females between the ages of 35 and 44 years in 33 census enumeration districts within the city of Jackson, Mississippi. 199 women of the desired age fully participated in the study, which included collection of a 24 hour urine specimen, six blood pressure measurements, and a family and personal history including a history of medication. Twenty-seven (13.6%) were taking antihypertensive medication. Those patients on antihypertensive therapy had a significantly higher sodium excretion (1 0.9 mEq per day versus 1?2.75 mEq for those not on therapy, $p < 0.0?$). An indication that the usual antihypertensive therapy included a diuretic was given by the lower calcium excretion (2. 6 mEq per day versus 3.14 mEq for those not on therapy ($p < 0.10 > 0.05$)) with a markedly increased sodium/calcium ratio 99.1 for those patients on therapy and 53.4 for those not on therapy ($p < 0.01$). The difference in sodium excretion between those on therapy and those without therapy was especially pronounced in the individuals with diastolic blood pressure greater than 100, with eight individuals on therapy excreting 20? mEq sodium per 24 hours versus the excretion of 126 mEq per 24 hours in the 31 individuals with diastolic blood pressures greater than 100 mm Hg who were not on therapy. These findings suggested to us that the increased steady state sodium excretion was a consequence of the antihypertensive therapy, and as those with the diastolic pressure greater than 100 mm who were on therapy were excreting almost twice as much as those with diastolic pressure less than 100 mm Hg further suggested that the increased sodium intake was negating the antihypertensive effects of the therapy.

If the antihypertensive therapy, through its diuretic component, had produced enough sodium deprivation to increase the sodium appetite we would have a logical explanation for our findings. We have not tested this possibility directly, but we have measured the salt taste threshold before and two weeks after diuretic therapy in 54 newly diagnosed hypertensive patients. There was a significant ($p = 0.0?$) decrease in salt taste threshold as determined by the Wilcoxin Matched pairs sign rank test. Diastolic pressure change was correlated with salt taste threshold change in those who had a decreased salt taste threshold ($r = 0.6?6$, $p < 0.05$) but not in the increased salt taste threshold group ($r = 0.384$, n.s.).

We interpret the lowered salt taste threshold after diuretic therapy to represent the same phenomenon as a lowered salt preference level in salt-deprived rats. The relation between lowered salt taste threshold and increased salt consumption is not clear. Both changes may represent independent reactions to sodium deficiency. Yensen found lower salt taste threshold with sodium deprivation. Henkin and associates denies that sodium deprivation changes salt taste thresholds in humans. Henkin and associates apply a test solution to a small area of the tongue, other investigators have the individual take a mouthful of the test solution. Perhaps the difference in technique explains the difference in results.

Further evidence for the increased sodium excretion of the chronically treated patient on thiazide therapy is given by the study of Parijs and co-workers. Inspection of their data shows that patients on thiazide therapy excrete significantly more sodium after full time for equilibration than they did on placebo therapy. As one comes to a new equilibrium after a few days of thiazide therapy, this can only mean that they were taking in more sodium.

The important fact to us is that the antihypertensive (presumably diuretic) treated patient apparently acts like salt-deprived rats. Part of the behavioral change involves increased sodium intake. A sufficiently high sodium intake can block the antihypertensive effect of thiazide diuretics. Falls and Ford showed that going from 50 to 100 mEq sodium daily would block the antihypertensive effect of a fairly small dose of hydrochlorthiazide (50 mg daily), but 100 mg daily of hydrochlorthiazide was effective in lowering blood pressure at the higher sodium intake. Winer demonstrated that the addition of 20 Gm NaCl per day blocked the blood pressure lowering effect of the thiazide diuretic. Our results from Study

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operative cardiac surgical patients J Thorac Cardio vasc Surg 56 271 1968
52 Litwak R S Kuhn L A Gadboys H L Lukban S B and Sukurai H Support of myocardial performance after open cardiac operations by rate augmentation J Thorac Cardiovasc Surg 56 484 1968
53 Lajos T Z Pacemaker wire extension for permanent and temporary pacing Ann Thorac Surg 15 207 1973
54 Parsonnet V Cuddy T E Escher D J W Furman S Morse D Gilbert L and Zucker I R A permanent pacemaker capable of external non invasive programming Trans Am Soc Artif Intern Organs 29 224 1973
55 Bruce R A Blackmon J R Cobb L A and Dodge H T Treatment of asystole or heart block during acute myocardial infarction with electrode catheter pacing Am Heart J 69 460 1965
56 Chatterjee K Harris A and Leatham A The risk of pacing after infarction and current recommendations Lancet 2 1061 1969
57 Godman M J Lassers B W and Julian D G Complete bundle branch block complicating acute myocardial infarction N Engl J Med 282 237 1970
58 Norris R M Heart block in posterior and anterior myocardial infarction Br Heart J 31 352 1969
59 Resnekov L and Lipp H Pacemaking and acute myocardial infarction Progr Cardiovasc Dis 14 475 1972
60 Christiansen I Haghfelt T and Amtorp O Complete heart block in acute myocardial infarction drug therapy Am Heart J 85 162 1973
61 Hatee L and Rokseth R Conservative treatment of AV block in acute myocardial infarction Br Heart J 33 595 1971
62 Imperial E S Carballo R and Zimmerman H A Disturbances of rate rhythm and conduction in acute myocardial infarction Am J Cardiol 5 24 1960
63 Lown B Hood W B Fakhro A M Kaplinsky E and Roberge G Unresolved problems in coronary care Am J Cardiol 20 494 1967
64 El Sherif N Tachycardia and bradycardia dependent bundle branch block after acute myocardial ischemia Br Heart J 36 291 1974
65 Hass J Mechanisms of ventricular arrhythmias associated with myocardial infarction Am J Cardiol 24 800 1969
66 Atkins J M Leshin S J Blomquist G and Mullins C B Ventricular conduction blocks and sudden death in acute myocardial infarction N Engl J Med 288 281 1973
67 Gould L Venkataraman K Mohammad N and Gomprecht R F Prognosis of right bundle branch block in acute myocardial infarction J A M A 219 502 1972
68 Fisher J Unpublished data
69 Narula O S Scherlag B J Samet P and Javier R P Atrioventricular block localization and classification by His bundle recordings Am J Med 50 146 1971
70 Vera Z Mason D T Fletcher R D Awan N A and Massumi R A Prolonged His Q interval in chronic bifascicular block Relation to impending complete heart block Circulation 53 46 1976
71 Altschuler H Fisher J and Furman S Unpublished data
72 Bilitch M Cosby R S and Cafferky E A Ventricular fibrillation and competitive pacing N Engl J Med 276 598 1967
73 Preston T A Anodal stimulation as a cause of pacemaker induced ventricular fibrillation Am Heart J 86 366 1973
74 Chatterjee K Sutton R and Davies J G Low intracardiac potentials in myocardial infarction as a cause of failure of inhibition of demand pacemakers Lancet 1 511 1968
75 Preston T A Temporary unipolar pacing using a dual cathode J Electrocardiol 9 193 1976

substantial. The average operative mortality rate of published reports is near 10 per cent. As with medical therapy, however, the success rate is improving and in at least some medical centers the present mortality rate is clearly less than 10 per cent. But regardless of the absolute numbers and the varied success of particular medical centers the risk of urgent bypass in patients acutely ill with coronary insufficiency is almost certainly greater than the risk of scheduled elective bypass in stable patients. Therefore if it is possible without death or permanent loss of myocardial tissue stabilization of the patient would seem preferable especially in hospitals less accustomed to mobilization under emergency conditions in off hours.

A major difficulty is the fact that there are not and never will be any single values for the incidence of myocardial infarction or of death from either form of therapy. The best information we can expect to possess is the immediate *past* experience of a *specific* medical center with a *defined* type of patient. The prognosis depends very much on the definition of the syndrome or the subgroup of patients under consideration. For that reason and others comparison of results from different studies will continue to be frustratingly inconclusive. The most productive approach would seem to be to define the particular patient population under study and to separate this population into treatment groups which are truly comparable at the onset. The importance of these steps has been recognized for some time. The optimal method of achieving comparability is by random allocation of patients (after each is deemed surgically acceptable). Even then the conclusions may pertain with certainty only to the medical center and the patient population involved. Hopefully the results of several different randomized studies will be consistent enough to be combined. The conclusions then could be applied broadly with even greater confidence than in the case of a single large study.

In the meantime the following approach to the management of patients with acute coronary insufficiency would be consistent with the information now available. This plan is not advocated as necessarily better than performing coronary bypass urgently on all patients. It simply is one alternative that is at least equally justifiable on the basis of existing data.

This questio [illegible] be sat[illegible] rily settled only by [illegible] number of [illegible] identif[illegible] experimental comparison of th[illegible] different [illegible] modes [illegible]

The patient is put to bed in an Intensive Care Unit. Propranolol is used or not used depending upon the severity of angina prior to hospitalization as well as upon other clinical considerations. Many patients will have no further symptoms after hospitalization and most others can be stabilized by propranolol. Only a small fraction of patients will continue to have angina and ischemic ECG changes despite several days of intensive medical therapy. They are the only ones in whom coronary bypass surgery is carried out on an urgent basis (while rather abruptly decreasing their propranolol dose). The other patients who were successfully stabilized in the Intensive Care Unit are progressively ambulated over a period of several days and are discharged from the hospital in two to three weeks. Some will maintain a satisfactory asymptomatic state on continued medical treatment. In one small experience bypass surgery was thus avoided in approximately half of the patients. Other patients who initially stablizied in the hospital can be expected to develop incapacitating exertional angina following discharge. Elective surgery is recommended in these patients because of its demonstrated effectiveness in relief of disabling angina.

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REFERENCES

1. Gazes P C, Mobley F M, Jr, and Faris H M, Jr: Preinfarction (unstable) angina: a prospective study, ten year follow up, prognostic significance of electrocardiographic changes. Circulation 48:331, 1973.
2. Fischl S J, Herman M V, and Gorlin R: The intermediate coronary syndrome: clinical angiographic and therapeutic aspects. N Engl J Med 288:1193, 1973.
3. Selden R, Neill W A, Ritzmann L W, Okies J E, and Anderson R P: Medical versus surgical therapy for acute coronary insufficiency: a randomized study. N Engl J Med 293:1329, 1975.
4. Krauss K R, Hutter A M, Jr, and DeSanctis R W: Acute coronary insufficiency: course and follow up. Circulation 45 (Suppl 1):66, 1972.
5. Bigelow J: Nature in disease. Boston, 1854, Ticknor and Fields, p. 33.

Augmentation of auscultatory and echocardiographic mitral valve prolapse by atrial premature depolarizations

The mid systolic click late systolic murmur prolapsing A-V valve syndrome has been the focus of increasing attention in the past decade and has recently been reviewed by Barlow and Pocock. Several physiological and pharmacological interventions have been described which are capable of intensifying and/or prolonging the murmur. Although the mechanisms

I support such a blunting or blocking effect It may be that one frequently is in an escalation race each increase in diuresis may be met by a further increase in sodium intake

The two types of evidence which we have presented do not give completely solid evidence that increased salt appetite and sodium intake occurs in the diuretic treated hypertensive patient However the adaptive changes to sodium deprivation in other species involves change to conserve sodium loss and to increase sodium intake and the results cited above suggest that humans also are responding to sodium depletion by increasing their sodium intake

The authorities who would deny the necessity of sodium restriction in the treated hypertensive may frequently be pragmatically correct we suggest that this is a quantitative question The variables probably include the patient s basal salt intake the sensitivity of his blood pressure to salt deprivation the amount that the patient increases his salt intake and the dose of diuretic that the physician is willing to prescribe It seems likely that the behavioral change of increased salt ingestion may at times defeat the therapeutic attempts of the physician and that sodium restriction should remain part of the physician s advice to patients receiving diuretics for hypertension If the patient is not responding well to minimal therapy then monitoring of the patient s 24 hour urine sodium excretion may help to guide the physician and patient to the correct therapy

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REFERENCES

1 Ambard L and Beaujard E Causes de l hypertension arterielle Arch Gen Med Paris 1 520 1904
2 Allen F M and Sherrill J The treatment of arterial hypertension J Metabol Res 2 429 1922
3 Kempner W Treatment of hypertensive vascular disease with rice diet Am J Med 4 545 1948
4 Kincaid Smith P McDonald I Hua A Laver M D and Fank P Changing concepts in the management of hypertension Med J Aust 1 327 1975
5 Editorial Salt and hypertension Lancet 1 1325 1975
6 Denton D A Evolutionary aspects of the emergency of aldosterone secretion and salt appetite Physiol Rev 45 245 1965
7 Langford H G and Watson R L Electrolytes and hypertension in epidemiology and control of hypertension edited by O Paul Miami 1975 Symposium Specialists pp 119 130
8 Lambert B A and Kuhlback G Effect of chlorthiazide and hydrochlorthiazide on the excretion of calcium in urine Scand J Clin Lab Invest 11 351 1959
9 Yenson R Some factors affecting taste sensitivity in man II Depletion of body salt Q J Exp Psychol 11 230 1959
10 Henkin R I Gill J R Jr and Bartter F C Studies of taste thresholds in normal man and in patients with adrenal corticoid insufficiency The role of adrenal cortical steroids and of serum sodium concentration J Clin Invest 42 727 1963
11 Parijs J Joosens J V Van der Linden L Verstreken G and Amery A K P C Moderate sodium restriction and diuretics in the treatment of hypertension AM HEART J 85 22 1973
12 Fallis N and Ford R V Electrolyte excretion and hypertension response J A M A 176 581 1961
13 Winer B M The antihypertensive actions of benzothiadiazines Circulation 23 211 1961

Proper management of acute coronary insufficiency—the burden of proof

There is much enthusiasm now for urgent coronary bypass surgery as the proper therapeutic approach to patients with acute coronary insufficiency The popularity of this attitude rests on three principal supports whose validity should be questioned These are (1) a conviction that medical therapy is ineffective (2) a surgical mortality rate that is referred to as small in comparison to the peril of withholding surgery and (3) a bias that given a threatening situation vigorous action is inherently superior to an (apparently) less dramatic strategy

The study by Gazes and associates presented a grim outlook for patients with acute coronary insufficiency e g 21 per cent experienced a myocardial infarct and 9 per cent died within three months and the prognosis was even worse in the subgroup of patients with continued bouts of chest pain after hospitalization Those data helped to establish a receptive mood for a fresh therapeutic approach and they still often are quoted as the medical treatment results against which surgery is to be compared The patients however were treated prior to the use of propranolol and the data can no longer be considered representative of medical therapy Present methods of intensive medical therapy including propranolol administration succeed in resolving the acute illness in the great majority of patients The group of patients treated medically sometimes includes those rejected from surgery because of poor myocardial function or other reasons which themselves influence prognosis adversely This is another factor which has unfavorably misrepresented the outcome of medical treatment When a more homogeneous group comprised only of surgically acceptable patients was randomly allocated to medical or surgical treatment the incidences of death and myocardial infarction were comparatively low in medical patients

How effective is urgent coronary bypass in preventing threatened infarction or death? Detection of intraoperative myocardial infarction is fallible but its incidence certainly is

chamber size associated with premature contraction the additional possibility of enchanced mitral regurgitation due to a VPD induced alteration in the contraction sequence of the papillary muscles and ventricular wall cannot be excluded With an APD exhibiting no ventricular aberrancy the papillary muscle contraction sequence is normal and hence the mechanism of increased prolapse in our case can only be reduced ventricular chamber size Careful auscultation during atrial premature beats (which are frequent in this syndrome) as with auscultation in the upright posture may allow verification of the physical findings of the mid systolic click late systolic murmur syndrome when more casual evaluation in the supine position does not This may allow some patients to avoid the noxious and/or potentially hazardous effects of pharmacological interventions which may otherwise be necessary for diagnostic clarification

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REFERENCES

1. Barlow J B and Pocock W A The problem of non ejection systolic clicks and associated mitral systolic murmurs Emphasis on the billowing mitral leaflet syndrome Am Heart J 90 636 1975
2. Barlow J B Bosman C K Pocock W A and Marchand P Late systolic murmurs and non-ejection ("mid late") systolic clicks An analysis of 90 patients Br Heart J 30 203 1968
3. Epstein E J and Coulshed N Phonocardiogram and apex cardiogram in systolic click late systolic murmur syndrome Br Heart J 35 260 1973
4. Gulotta S J Gielco L Padmanabhan V and Miller S The syndrome of *systolic click murmur and mitral* valve prolapse—a cardiomyopathy? Circulation 49 717 1974
5. Fontana M E Pence H L Leighton R F and Wooley C F The varying clinical spectrum of the systolic click late systolic murmur syndrome A postural auscultatory phenomenon Circulation 41 807 1970
6. Towne W D Rahimtoola S H Sinno M Z Loeb H S Rosen K M and Gunnar R M The effects of right atrial and ventricular pacing on the auscultatory findings in patients with mitral valve prolapse Circulation 51 988 1975
7. Dillon J C Haine C L Chang S and Feigenbaum H Use of echocardiography in patients with prolapsed mitral valve Circulation 43 503 1971
8. Kesteloot H and VanHoute O On the origin of the telesystolic murmur preceded by a click *Acta Cardiol (Brux)* 20 19 1965
9. Perloff J K and Roberts W C The mitral apparatus Circulation 46 227 1972

Of chronic adhesive pericarditis

Chronic adhesive pericarditis is being produced in patients by the tens of thousands each year in the U.S.A as well as in the world at large It is impossible to do coronary bypass surgery without pericarditis developing in 100 per cent of the patients who survive The raw (non epithelized) venous segments which are continuously rubbing the surfaces of the pericardium plus the operation itself can be expected to produce pericarditis even in the patients in whom the pericardium is closed at surgery And surely pericarditis will develop in those patients in whom the pericardium is left open The natural history pathology pathophysiology and management of chronic pericarditis shall evolve in time as the patients are observed and the hearts are studied at autopsy The etiology of this type of pericarditis will be known its onset precisely dated and the course and natural history recorded. The incidence of pleuropericardial adhesions mediastinopericardial adhesions concretio cordis calcification hemodynamic and other pathophysiologic phenomena loss of protein from the gastrointestinal tract and nutritional changes will all be among the abnormal states to be observed More will become known about pericarditis especially chronic adhesive pericarditis in the near future than ever before The opportunities should not be lost That they will be lost is extremely unlikely as the patients will force the studies upon the medical profession

Whether or not the pericarditis itself is good for the patient will be determined and the detrimental effects likewise will become known. Whether or not this disease state is fair exchange for the ischemic heart disease which prompts its production will also be learned

Are we embarking on an unknown course? And is this necessary or wise? Can the answers be determined in advance or the incidence controlled and studied before the consequences become too extensive? Chronic adhesive pericarditis is a universal inevitable "side effect" of the therapeutic agent—coronary bypass surgery

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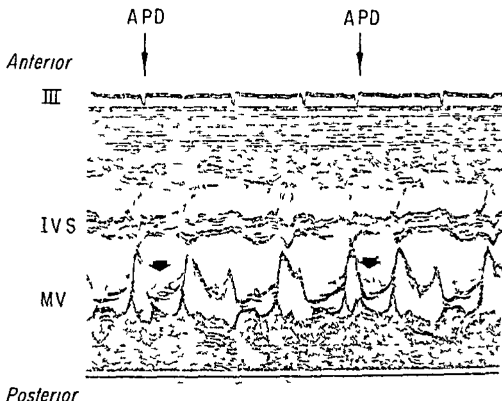


Fig 1 Echocardiogram revealing mitral valve prolapse during atrial premature beats and during beats of sinus origin *III* = standard Lead III *IVS* = intraventricular septum *MV* = mitral valve Arrows denote contractions induced by atrial premature depolarizations and maximum degrees of prolapse

by which these interventions achieve their effect are not singular many operate at least in part by decreasing end diastolic ventricular chamber size (upright posture Valsalva maneuver amyl nitrate inhalation for example) The resulting alterations in valve leaflet chordal and papillary muscle position and tension allow earlier and greater excursion of the prolapsing leaflets We recently noted a spontaneous physiological event which also prolongs and intensifies the prolapse and resultant murmur—atrial premature depolarizations (APD)—as is exemplified in the following case To our knowledge this observation has not been described previously although its possibility has been previously considered

B W is an extremely anxious 36 year old housewife with a long history of palpitations who came to the emergency room because of intermittent transient (3 to 90 minute) episodes of substernal pressing chest discomfort for one week Physical examination revealed a slender 5 feet 10 inches white female in no distress Blood pressure was 130/80 pulse 88 with 8 premature beats/minute Cardiac examination revealed normal heart size thrust first and second sounds no gallops or rubs but the following additional phenomena In the supine position with each cardiac cycle there was a barely audible mid systolic click followed by a Grade I/VI apical late systolic murmur ending at A_2 When the cardiac contraction was initiated prematurely by an ADP the click occurred earlier in systole and the murmur became longer and intensified to Grade II/VI In the standing position with each cardiac cycle there was a soft mid systolic click followed by a Grade III/VI apical late systolic murmur ending at A The click occurred earlier and the murmur was longer than in the supine position When the cardiac contraction was initiated prematurely by an APD the murmur intensified further and began earlier in systole The chest x ray was normal and the electrocardiogram was remarkable only for shallow inferior T wave inversions and flattened T waves in Leads V and V Phonocardiography was refused by the patient

M mode echocardiography was performed utilizing a Smith Kline Ekoline 20A ultrasonoscope with a 2 25 MHz focused 13 mm diameter transducer coupled to a Honeywell 1856 strip chart recorder It revealed (Fig 1) a mid late systolic posterior movement of the posterior mitral valve leaflet (typically seen in this syndrome[7]) beginning 265 msec after the Q wave on the ECG during contractions of sinus node origin The left ventricular end diastolic diameter was 42 mm In the systolic intervals initiated by APDs (see arrows) the posterior prolapsing movement occurred prematurely (beginning 204 msec following the Q wave on the ECG) was holosystolic appeared to have a greater posterior excursion and followed a left ventricular end diastolic diameter of 38 mm Of interest is the fact that echocardiograms of the patient s mother and sister were both normal

The APD as this case exemplifies is yet another instigator capable of exacerbating the physical and echocardiographic findings associated with the mitral valve prolapse syndrome By initiating ventricular systole prematurely the APD induces ventricular contraction before ventricular filling is complete and hence at a smaller chamber size than occurs with sinus beats As with the other interventions which decrease end diastolic ventricular dimensions the result with the APD is also earlier and more pronounced posterior valvular prolapse While prolongation of the murmur in this syndrome following ventricular premature depolarizations (VPD) has been previously described (with phonocardiographic but not echocardiographic documentation) and has likewise been presumed to result from a smaller end diastolic

by measurement of the cardiothoracic ratio This difficulty has been noted before and it has been suggested by Simon that rather than continue to use this ratio we should in tead rely on absolute measurements of transverse heart diameter i e the sum of the measurement of the furthest projections of the heart shadow to the right and left of the midline Simon stated that any heart larger than 15 5 cm is probably a pathologically enlarged heart unl ss the patient is tall very muscular heavy and in an occupation needing much muscular effort

We have recently studied quantitatively various parameters of the chest radiographs of 100 normal individuals including the transverse heart diameter and find this to be true The distribution of heart size was found to follow a normal Gaussian pattern with a range of 8 50 to 16 00 cm in the male (median 12 5 cm) and 9 5 to 14 00 cm in the female (median 11 to 12 cm) The only individual with a transverse heart diameter greater than 15 5 cm was overweight (86 kilograms) though not tall (163 cm)

Thus although the early enlargement of small hearts cannot be detected in this way the use of such absolute criteria may go some way to solving Dr Burch s problem

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REFERENCES

1 Simon G Principles of chest x ray diagnosis 3rd ed London 19 1 Butterworth & Co Ltd
2 Williams A J and Simon G Some parameters of the normal chest x ray (In preparation)

An appeal for data

To the Editor

For a biography of Dr Alton Ochsner of Ochsner Clinic New Orleans opinions evaluations anecdotes reminiscences photos and any other relevant material are urgently needed Photos will be carefully handled and will be returned All material will be gratefully received by

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Survival after aortic valve replacement

To the Editor

It is tragic that the important question *Which patients will benefit from cardiac valve replacement?* continues to be shrouded in mystery because of *poorly designed* clinical trials and inaccurately reported results Sufficient statistical methodology exists to allow clinical investigators to consider both the ethical responsibility to administer the best available therapy and the scientific responsibility to conduct a *proper* evaluation

Advances in valve replacement have been impressive However excessive enthusiasm has swung the pendulum too far from center The risk benefit ratio is sometimes derived by comparing an unrealistic expectation of success with the most pessimistic estimate of the natural course

The relevance of this editorial statement by Dr Arthur Selzer is illustrated in Long term survival following aortic valve replacement in the March 19 6 issue of the AMERICAN HEART JOURNAL Dr Roberts and his associates assert that survival of patients with symptomatic aortic stenosis and/or regurgitation is clearly improved when they have had replacement of the aortic valve This premise is supported by a figure showing three lines one purporting to show the "overall survival of the entire patient group " another representing the natural history of untreated aortic valve disease and the third representing a comparison population The line representing the "overall survival of the entire patient group" actually represents, at best the "surviving patient group" the 24 patients who constitute the hospital mortality group were not included The text states that 18 of the initial 95 survivors of aortic valve replacement died within the first two years following surgery—a 19 per cent mortality rate the figure shows this percentage at three years

The control group used for comparison with the patients surviving aortic valve replacement was taken from a study completed 21 years before the completion of the aortic valve replacement study Doctors Gehan and Freireich have warned Using patients from a previous study *could* be misleading if a relatively long interval had elapsed between studies (say greater than three years) or if it could be demonstrated that important changes had taken place in clinical investigators, type of patients or therapy Patients from a previous study should not be used as selected controls in such circumstances and a randomized prospective study is recommended

Dr Roberts and his associates compared their patient group to patients receiving no treatment which is only one of the three alternate choices—no treatment less drastic surgical therapy or medical management A comparison can be made between the total surgical group and a group of medically treated patients (Fig 1) This is an admittedly poor comparison as no attempt can be made to compare the patients in the two groups as to severity of disease etiology of disease age sex or other important factors affecting mortality The two groups can only be compared in that the patients in both groups were symptomatic Though *imprecise* this comparison of surgically treated patients and medically treated patients is in accord with Dr Selzer s editorial statement that valve replacement clearly prolongs life in the middle aged or elderly patient with aortic stenosis who is symptomatic and whose symptoms are related to valve obstruction However no such conclusion is obvious for patients with aortic insufficiency

It is assumed that the mortality of the surgically treated patients is evenly distributed as Dr Roberts and his associates report Survival in the stenotic regurgitant and combined groups was nearly identical " This statement is in contrast to the data in their Fig 4 representing the survival of these groups which presents significantly greater mortality for the patients with aortic regurgitation alone and in combination with aortic stenosis than the mortality presented for patients with aortic stenosis alone

The important question remains unanswered *For which patients does cardiac valve replacement affect the natural history of valvular heart disease in a positive way?* The National Heart and Lung Institute has allocated 51 million dollars for clinical trials in 1976 It is imperative that the

Letters to the Editor

Concerning rheumatic fever and rheumatic heart disease

To the Editor

I cannot but agree with Dr Ward's position (Observations on the diagnosis of isolated rheumatic carditis AM HEART J 91 545 1976) about the obvious inadequacy of the Jones criteria of diagnosis as it pertains to both rheumatic fever (R F) and rheumatic heart disease (R H D) But since his paper implies a dramatic reevaluation of R F and R H D I think it will be of interest to present some comments

There is no doubt that viral disease can closely simulate R F and R H D When the knowledge of connective diseases made necessary the last reevaluation of the Jones criteria virology was still a newborn science But time after time certain undeniable data appeared establishing the incidence of viral diseases with general and cardiac manifestations which are sometimes quite difficult to distinguish from R F or R H D

Too often the diagnosis is cursory either because the practitioner does not yet know the newer concepts or because viral investigations are too sophisticated and too expensive

Another clue to the likely role of viral disease in R F and R H D is that despite many years of effective prophylaxis the appearances of so called R H D are more numerous than we have been led to expect I therefore believe that a great number of so called concealed episodes of R F are actually viral manifestations that induce secondary cardiac disease

The French theory of minor streptococcic syndrome based on the presence of two minor criteria and a recent streptococcic infection appears to be much more tentative

Dr Ward's remarks have to be taken particularly seriously with regard to the prevalence of R F in tropical countries Indeed R F and its complications have nowadays practically become tropical diseases because prophylaxis is so much better organized in developed countries that they have almost been stamped out there the opposite however is the case in the still undeveloped tropic nations

Viral diseases are not uncommon in tropical countries Coxsackie B viruses have been encountered but we must emphasize the incidence of arbovirus with a well established cardiac tropism

On the other hand we now know about helminthic rheumatism caused by *Strongyloides stercoralis* which can be associated with arthritis fever and abdominal pain and which can simulate R F Furthermore we must examine very carefully the possibility of sickle cell disease (S C D) before we assume R F or R H D Many authors from Klinefelter to Mazzara and colleagues have exhaustively shown that different aspects of S C D (SS AS or SC) can be very similar to R F and R H D S C D is practically limited to black people and this same population also falls victim to R F so that the coexistence of both diseases is not as rare as was previously held

The signs of S C D can include fever pseudo arthritis abdominal pain cardiac murmurs (almost always systolic but sometimes diastolic as well) P R enlargement and cardiomegaly Also infections are very frequent in S C D so that a rise in A S O titer is not uncommon

To conclude my opinion is that the classic conception of R F and R H D based on the Jones criteria appears every day less suitable when we are confronted with other diseases that were considered rare before This is true for most viral diseases but S C D and some helminthic diseases should especially be better known Because the Jones criteria have been reviewed since connective diseases had already been discovered it seems that now is the time for a new reevaluation of these criteria

Science makes it a point of honor to progress by endless self examination again and again the advent of new concepts seems to make things more complex but after a transitional period the data are in the end better understood This is where we now stand with R F and R H D Dr Ward's constructive criticism of the lack of reliability of the Jones criteria lends support for the use of a trustworthy noninvasive method to investigate intracardiac elements With this new method (echocardiography) we are in a position to detect the valvular alteration characterizing R H D

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REFERENCES

1. Doury P et al Anguillulose et manifestations articulaires Ann Med Interne 125 743 1974
2. Fidelle J E and Toumieux M C Classification des syndromes post streptococcique *in Journee Parisiennes de Pediatrie* Paris 1969 Flammarion p 398
3. Klinefelter H F The heart in sickle cell disease Am J Sci 203 34 1942
4. Mazzara J T et al Coexistence of sickle cell anemia and rheumatic heart disease N Y State J Med 71 246 1971
5. Nagaratnam N et al Arboviru (dengue type) as a cause of acute myocarditis and pericarditis Br Heart J 35 204 1973
6. Obeyesekere I and Hermon Y Myocarditis and cardiomyopathy after arbovirus infections (dengue and chikungunya fever) Br Heart J 34 821 1972
7. Obeyesekere I and Hermon Y Arbovirus heart disease Myocarditis and cardiomyopathy following dengue and chikungunya fever—A follow up study AM HEART J 85 186 1973
8. Ayuthya P S N Jayavasu J and Pongpanich B Coxsackie Group B virus and primary myocardial disease in infants and children AM HEART J 88 311 1974
9. Smith W G Coxsackie B myopericarditis in adults AM HEART J 80 34 1970

Radiographic assessment of cardiac enlargement

To the Editor

In his comments on the radiographic assessment of cardiac enlargement (AM HEART J 92 264 1976) Dr Burch interestingly points out the problem of the shrinking senile chest and the difficulty that arises in assessing cardiomegaly

with predominant aortic stenosis those with combined lesions and those with aortic regurgitation from the sixth to the ninth years However because of the small number of patients no statistical significance was present

Mrs Horton and Dr Spodick question the use of data from a previous study as a control group However available information concerning the natural history of symptomatic aortic valve disease would appear to preclude any justification for a randomized study While we wholeheartedly endorse such studies, they might best be used to determine the optimal timing for valve replacement and evaluation of different prosthetic devices It should be pointed out that all of our patients were operated on because despite optimal medical therapy they showed deterioration and progression both clinically and by laboratory studies

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REFERENCES

1 Frank S Johnson A and Ross J Jr Natural history of valvular aortic stenosis Br Heart J 35 41 1973
2 Ross J Jr and Braunwald F Aortic stenosis Circulation 38 (Suppl V) V 61 1968
3 Spagnuolo M Kloth H Taranta A Doyle F and Pasternack B Natural history of rheumatic aortic regurgitation Criteria predictive of death congestive heart failure and angina in young patients Circulation 44 368 1971

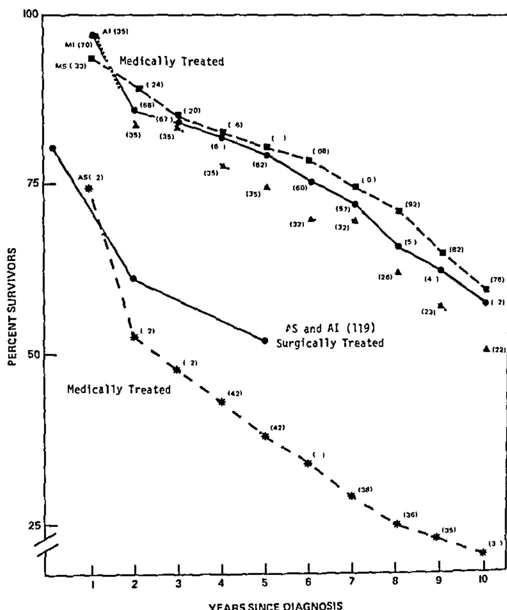


Fig 1 Per cent survival of patients with mitral and aortic valve disease treated medically and with aortic valve disease treated surgically

implementers of these clinical trials accept their responsibility to design prospective investigations which will reliably determine the criteria for identification of patients who will best benefit from cardiac valve replacement

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REFERENCES

1 Gehan E A and Freireich E J Non randomized controls in cancer clinical trials N Engl J Med 290 198 1974
2 Selzer A Cardiac valve replacement An unanswered question Am J Cardiol 37 322 1976
3 Roberts D L DeWeese J A Mahoney E B and Yu P N Long term survival following aortic valve replacement AM HEART J 91 311 1976
4 Duvoisin G E and McGoon D C Aortic valve replacement with a ball valve prosthesis Arch Surg 99 684 1969
5 Bergeron J Abelmann W H Vazquez Milan H and Ellis L B Aortic stenosis—Clinical manifestations and course of the disease Arch Intern Med 94 911 1954
6 Rapaport E Natural history of aortic and mitral valve disease Am J Cardiol 35 221 1975
7 Corday E and Corday S R Letters to the Editor Am J Cardiol 37 419 1976

Reply

To the Editor

We appreciate the comments of Mrs Horton and Dr Spodick regarding our recent article

They are correct that Fig 1 of our article omitted the hospital mortality group This graph was intended to lay emphasis on long term results As mentioned in the text a changing mortality rate occurred over the years included in the study We felt it was easier for the reader to compare the data to his own personal experience using this format

Fig 4 shows an apparent difference between the patients

This publication of the proceedings of a symposium held in Paris during Dec 12 and 13 1974 on the clinical pharmacology of drugs used in the treatment of angina pectoris Most of the participants were from France The studies reported are concerned mainly with vasodilator agents and beta blockers The discussions of pharmacology and coronary artery response are both basic and clinically directed The changes in coronary blood flow produced by these drugs are discussed Metabolic effects of propanolol on the ischemic myocardium and mechanism of action of nitrates and beta adrenergic blockers are among the presentations. The symposium is directed primarily toward pharmacologists and clinical pharmacologists The illustrations are in general clear and well selected The various papers are documented by a selected bibliography The book should interest all pharmacologists internists and cardiologists All papers are in French except for a few that are in English This is a good book on an important subject

Books received

The Arterial Hypertensive Disease A Symposium Paris 1976 Editions Masson 414 pages

Bibliography on Zinc in Biological Systems Compiled by John W Gardner Reed M Izatt and James J Christensen Provo Utah 1976 Brigham Young University Press 3 8 pages. Price $9 95

Symposium on Development of Upper Respiratory Anatomy and Function Edited by James F Bosma M D and Jane Showacre Ph D Washington D C 1976 U S Dept of Health Education and Welfare NIH DHEW Publication No (NIH) 75 941 269 pages Price $7 10

Self Assessment in Clinical Cardiology 2 Edited by Michael S Gordon M D Chicago 1976 Year Book Medical Publishers Inc 349 pages

Nutrition and Cardiovascular Disease Edited by Elaine B Feldman M D New York N Y 1976 Appleton Century Crofts Inc 293 pages Price $14 50

The Conduction System of the Heart Structure Function and Clinical Implications Edited by H J J Wellens M D K I Lie M D and M J Janse M D Philadelphia 1976 Lea & Febiger Publishers 708 pages

Obviously the conduction system of the heart is an extremely important structure of the heart An intact normal functioning conduction system is necessary for proper function of the cardiac pump Proper timing of the contraction of each chamber and all parts of each chamber is necessary for normal cardiac function The book is dedicated to Dr Dirk Durrer and is based upon a workshop conducted in the spring of 1975 in Amsterdam The many contributors from several nations of the world discuss anatomy and electrophysiology of the conduction system impulse formation the sinus node and atrium the A V junction and bundle branches and ventricle the WPW syndrome and myocardial infarction The many papers should interest all cardiologists because of the importance of the role of disturbances in cardiac rhythm in cardiac disease These many presentations review the common problems of disturbances in function of the conduction system This is a good book edited by outstanding cardiologists of Amsterdam Dr Durrer should feel honored to have the book dedicated to him

Intensive Care Edited by John Joakim Skillman M D Boston 1973 Little Brown & Company 609 pages

Intensive care centers exist in practically all hospitals of the world They are no better than the people who are responsible for their operation This book edited by Skillman is an excellent source for study of intensive care of seriously ill patients It is surgically oriented Most books on this subject have been medically directed The SICU is extremely important in the care of the patient who undergoes complex cardiac surgical operations and patients with cardiac disease subjected to major surgical operations The importance of teamwork is emphasized as well as a thorough knowledge of pathophysiology and management of disturbances in physiology The book should interest all cardiologists as well as all surgeons not only cardiac surgeons The book is worth owning It is practical and clearly written

Clinical Cardiovascular Physiology Edited by Herbert J Levine New York 1976 Grune & Stratton Inc 945 pages $52 50

This book of about 1 000 pages edited by Dr Herbert Levine contains a rather extensive review of the common pathophysiologic problems in clinical cardiology The discussions are clearly presented and each chapter contains a fairly extensive selected bibliography The contributors tend to present the pathophysiologic disturbances in fair detail but always with clinical implications in view The 24 chapters include a review of electrophysiology hemodynamic phenomena in the normal and failing heart contraction of heart muscle as related to its structure renal function in congestive heart failure digitalis and cardiomyopathy The book contains an enormous amount of information that is useful to clinicians who manage a large number of patients with heart disease Students house staff and trainees in cardiology will find this to be a useful and thought provoking book It must be studied critically since each chapter definitely reflects the respective author s opinions and approach to these complex cardiologic problems The book is highly recommended to all physicians who manage cardiac disease

Bedside Cardiology ed 2 Jules Constant M D Boston 1976 Little Brown & Company 443 pages

This book emphasizes the need for better training in bedside cardiology But when one refers as on the top of p 267 to the shape of a murmur then the reader is forced to wonder how bedside this presentation is Further as is evident the author is referring in this instance to the phonocardiographic recording and the time course of the pressure gradient across the mitral valve orifice but the explanation falls short of a clear explanation or reference to the recorded phonocardiogram which is not a routine bedside or office procedure The book consists of questions and answers concerning the bedside study of the patient A check list is presented for detailed history taking The questions related to the physical signs such as sounds arterial pulse etc do raise interesting ideas and thoughts The illustrations are simple and well selected Readers will find this book to be useful thought provoking and concerned with important bedside and office approaches to the study of the heart and circulation of patients

The Hemiblocks in Myocardial Infarction By Agustin Castellanos Jr and Robert J Myerburg New York 1976 Appleton Century Crofts 158 pages $11 75

This is a short book on hemiblocks a conduction disturbance which apparently has caused considerable confusion in ECG laboratories throughout the U S A An ECG diagnosis of hemiblock is too frequently made The ECG shown in Fig 12 p 21 of this book is a good example It would be difficult to differentiate this ECG from that of left axis deviation due to other causes such as a transverse heart with counterclockwise rotation along the longitudinal axis of the heart or from left ventricular hypertrophy The fidelity of direct ECG recorders is so poor that an error of 1 to 2 msec can readily occur in a QRS complex of the conventionally clinically recorded ECG This book consists of the authors concepts of the hemiblock as the syndromes are observed and diagnosed in patients with myocardial infarction The strict and reliable criteria for diagnosis pathogenesis and clinical significance of the hemiblock are yet to be defined This book does stimulate interest in the problems related to hemiblock but this reviewer cautions the reader to study this book critically and to employ the authors diagnostic criteria cautiously There is a need to study in detail more of the hearts at autopsy to learn if the diagnosis so frequently made by ECG is actually due to hemiblock or to some other cause This book is difficult to follow because of the numerous abbreviations many not generally used in other institutions Some criteria for diagnosis seem to be arbitrary e g the degree of left axis deviation of the QRS complex that indicates left anterior hemiblock (see p 5)

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American Heart Journal
May 1977 Volume 93 Number 5

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al therapy for coronary artery dısease
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G Pauker MD FACP FACC
ss.

'ıst decade has seen the coronary artery graft evolve into the most common form ıac surgery at many ınstitutıons Fueled by gh prevalence of coronary dısease ın this y this extraordinary growth of coronary y has been little checked by the scarcity of lled prospective studies designed to exam e efficacy of the coronary bypass graft as a of relieving pain prolonging life prevent yocardial infarction and improving ventric unction This JOURNAL as have others has a forum for discussion concerning these

his time only one conclusion seems clear nt data are not yet available about the erm effects of bypass surgery Indeed it a long time before consensus is reached In antime what shall today s physicians and ts do? Coronary surgery is available now ecisions must be made based on the best ow available The patient or the physician fers his decision until the final answer is y not survive long enough to learn that He is in effect opting for medical ther

eral easy solutions might be tried The ician cognizant of the need to insure rmed consent could summarize the present roversy for his patients tailor that summary to reflect the prognosis of each individual patient and place the burden of the decision on that patient by saying Only you can make this decision' Unfortunately few patients are equipped to comprehend the controversy sort out the details and arrive at a logical choice Most will either choose blindly or will take the second easy solution Doctor I just don t know Please tell me what I *should* do The physician may then suggest a therapeutic plan but all too often that suggestion will reflect the physician s own values and does not adequately reflect what would be best for a particular patient Of course this scenario is often bypassed when the physician does not consult the patient but summarily suggests 'The x rays show that you need surgery

In a recent article in the *Annals of Internal Medicine* one possible solution to this dilemma was proposed Decisions which must be made despite uncertainties in the data upon which the decision must be based can be approached by *decision analysis* Briefly the technique involves the explicit consideration of every possible outcome of each course of action For each of these potential outcomes the decision maker assigns a *probability* reflecting the relative likelihood of that outcome s occurrence and a *utility* reflecting the relative worth of that outcome The product of that probability and utility is a measure of the worth which that potential outcome would be expected to have The sum of these products for every potential ... eutic choice is the

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nt requests Stephen G Pa k M D N w England Medic l Hospital, 171 H rrison A Bosto M ss.

Seminar on Epidemiology and Prevention of Cardiovascular Diseases

The third 10 day seminar on the Epidemiology and Prevention of Cardiovascular Diseases will be held at Mount Snow Vermont from July 30 through August 12 1977 The primary goal of the seminar is to provide an intensive introduction to the epidemiology and prevention of the major cardiovascular diseases for interested and qualified professionals planning research or academic careers in this area Candidates must ordinarily be at the postdoctoral level with some residency training or its equivalent The seminar is sponsored by the American Heart Association and the National Heart Lung and Blood Institute There is no registration fee Deadline for receipt of applications is April 30 1977 For additional information please write Darwin R Labarthe M D Ph D American Heart Association 7320 Greenville Ave Dallas Texas 75231 Telephone (214) 750 5416

Doppler applications and New Developments

A symposium on Echocardiography with Doppler applications and New Developments will be held at Erasmus University Rotterdam The Netherlands on June 23 and 24 1977 This symposium has been initiated by the Committees on Bio Engineering and Monitoring of the Seriously Ill (Comité Recherches Medicales EEC) The purpose of the main program is to present to the clinically oriented participants current uses as well as limitations of echocardiography In addition lectures will be given on Doppler and New Developments in two dimensional imaging All lectures will be given in English A limited number of participants can be accepted Registrations must be made in advance The registration fee is 175 Dutch florins For further information write to N Bom Erasmus University P O Box 1738 Rotterdam The Netherlands

American Board of Internal Medicine Extension of examination

The American Board of Internal Medicine's certifying examination in the subspecialty of cardiovascular disease has been extended by an additional one half day This examination will now be administered on Tuesday October 18 1977 and on the morning of Wednesday October 19 1977 The registration period and all other requirements remain the same

XI International Congress of Angiology

The Czechoslovak Society of Cardiology and its Co
of Angiology will sponsor the XI International Cor
Angiology in Prague Czechoslovakia on July 2 throu
8 1978 Preliminary proposals for lectures should be
and applications should be secured from ANGI
GRESS 120 26 Praha 2 Sokolská 31 Czechoslovakia

Federation of Cardiology Congress

The Second ASEAN Federation of Cardiology Cong
be held from October 19 through 22 1977 at the Ph
Plaza Hotel Manila Philippines The Congress will b
the auspices of the Philippine Heart Center for Asia w
Philippine Heart Association Department of Foreign
Department of Health and the Department of Tourism
sponsors A variety of subjects pertaining to coronary
disease hypertension congenital heart disease cardiac
and valvular heart disease will be presented For adc
information concerning papers exhibits and regis
forms please write The Secretariat Second ASEAN I
tion of Cardiology Congress Philippine Heart Center fc
East Avenue Quezon City Philippines

International Symposium on Diagnosis and Treatment of Cardiac Arrhythmias

This international symposium organized by the
Society of Cardiology under the patronage of the E
Society of Cardiology will be held in Barcelona Spa
October 5 through 8 1977 The scientific program is co
of eight papers 8 round table discussions and 18 comr
tions dealing with drugs The scientific committee is co
of A Bayés de Luna Spain A Castellanos U S A
Aguilar Spain P Puech France F Sandoe Denmark
Sowton England and H J J Wellens The Neth
Please address all inquiries concerning the symposi
OTAC Congress Service Box 22 055 Barcelona 15 Sp

the patient's total clinical presentation what is the likelihood of each relevant outcome if only medical therapy is employed What is the likelihood if bypass surgery is undertaken?

This latter question is particularly difficult since reported series are often not comparable and since there is considerable variation among these series [7] The truly relevant data would bear on the prognosis of the *particular* patient at the particular institution where he is to be managed and where it is proposed that surgery be performed If that surgery is to be performed at a community hospital averaging just fifty bypass procedures annually are data that refer to a hospital performing over a thousand procedures each year relevant?

Thus the second major problem has become the lack of availability of *relevant* data This is just the point where the physician must employ his greatest skill After appropriate consultation and laboratory examination he must arrive at the best available *estimate* of the prognostic probabilities This process of estimation is difficult but it must clearly underlie *any* reasonable process of clinical decision making One advantage of the decision analysis model is that these estimates are *explicit* and therefore can be reexamined discussed and improved

The third problem encountered in this approach centers about the question of utilities—whose values should be used and how can they be obtained? Setting aside limitations imposed by resource constraints and overall societal cost the most logical source of these values is the patient himself since only he can express the burden which his angina represents and only he can evaluate the burden which early death would create

Since the proposed model is quite simple only ten outcomes need be considered Therefore one can examine the patient's attitudes toward each of the potential outcomes explicitly The method described in the *Annals* proposes the *lottery* technique for debriefing the patient of his values The essence of that technique is to offer the patient a series of simple choices between one hypothetically guaranteed outcome and a gamble between two more extreme alternatives By altering the odds of that gamble the physician can find a point where the patient is indifferent between the guaranteed outcome and the gamble The odds of the gamble at that point of indifference can be used to establish the utility of the guaranteed outcome In my experience such debriefing can be comfortably accomplished in less than one hour and most patients can understand and respond to the hypothetical alternatives

The analysis reported in the *Annals* demonstrates that the optimal decision for any individual patient cannot be determined solely from his clinical or angiographic presentation The past surgical results at the particular institution and the patient's own attitudes can easily alter the optimal choice and must therefore be considered

Let us consider an example Imagine two identical 50 year-old men with disabling angina not responsive to nitrates or beta adrenergic blockade Assume that they both underwent cardiac catherization and were shown to have lesions causing 70 to 80 per cent obstruction of both the proximal right coronary artery and the left anterior descending artery in its middle third with good distal run off in both vessels In both patients the ejection fraction was 30 per cent with segmental dysfunction along the anterior and posterior walls but without discrete areas of aneurysm.

Let us consider two hospitals where these patients might undergo bypass surgery *Hospital A* has had little experience in dealing with patients having marginal or depressed myocardial function while *Hospital B* has had broad experience with such patients Table I summarizes the best estimates of the probabilities of the various outcomes for these patients in each hospital

Mr Jones is a truck driver and is willing to take some risks to obtain pain relief whereas Mr Smith is an executive who would tolerate his disability if his life expectancy might be jeopardized by surgery Table I also summarizes hypothetical utilities that might be obtained from these patients The patients perceptions of the relative benefits and costs of the possible outcomes are reflected in these utilities

As pointed out above the expected value for surgical and medical therapy can be calculated by forming the product of the probability and the utility of each outcome and summing these products for surgical and medical therapy respectively These calculations are summarized in Table I for both Mr Jones and Mr Smith receiving treatment at either *Hospital A* or

Table I Calculation of expected values

Outcome	Probability		Utility		Expected value			
					Mr Jones at		Mr Smith at	
	Hosp A	Hosp B	Mr Jones	Mr Smith	Hosp A	Hosp B	Hosp A	Hosp B
Surgical therapy								
Peri operative death	15	05	0	0	0	0	0	0
Pain relief but fatal MI	25	30	60	85	15	18	21	26
Long term pain relief	20	40	100	100	20	40	20	40
Short term pain relief	13	09	80	85	10	7	11	8
Persistent pain and fatal MI*	13	09	40	70	5	4	9	6
Spontaneous relief of pain	04	01	80	85	3	1	3	1
Persistent pain	10	06	70	80	7	4	8	5
Surgical total	1 00	1 00			60	74	72	86
Medical therapy								
Persistent pain and fatal MI	50	50	50	80	25	25	40	40
Spontaneous relief of pain	10	10	90	95	9	9	10	10
Persistent pain	40	40	80	90	32	32	36	36
Medical total	1 00	1 00			66	66	86	86

Fatal MI refers to death within five years

expected value of that therapy The rational decision maker will select the therapy which has the greatest expected value

Whenever one attempts to use this approach to decision making, three questions become immediately apparent (1) which of the almost infinite array of possible outcomes should one consider? (2) where can one obtain the data which reflect the relative likelihood of occurrence of each of these outcomes? and (3) whose values should the utilities reflect? Each of these problems will be considered in turn with reference to the choice of therapy for coronary artery disease

The most difficult problem centers around the proper *structuring of the decision so that it* reflects the clinically significant facts but nevertheless remains manageable One might imagine an endless spectrum of possible outcomes cerebrovascular accidents after surgery debilitating postoperative musculoskeletal pain congestive heart failure Ideally all these possibilities should be considered but those potential outcomes which are extremely unlikely have little influence on the decision unless the utility of these outcomes is either extremely high or extremely low relative to the utility of the more likely events

The model proposed in the *Annals* does not attempt to be complete rather it tries to reflect the most likely outcomes in reasonably simple terms It considers only those outcomes which are considered in our current, empirical clinical decision making processes The model structures the potential outcomes along two dimensions—length of life and freedom from disabling angina The five year time horizon of the analysis reflects the limitations of presently available data about prognosis Survival is divided into three period (1) immediate death (2) death within five years and (3) survival beyond that time Disability is quantized into two states the presence or absence of disabling angina With the convention that death within five years is labelled Fatal MI, Table I summarizes the possible outcomes of both surgical and medical therapy Given a patient with disabling angina this model yields seven potential outcomes of surgical therapy and three possible outcomes of medical therapy

The next task is to estimate the likelihoods of these outcomes for the patient under consideration The patient s coronary anatomy and ventricular function must be assessed since prognosis is determined in large part by these variables Furthermore as pointed out elsewhere[5] additional clinical variables such as exercise tolerance segmental function the results of myocardial imaging and the presence of arrhythmias hypertension and co existing disease should all be considered The proposed model suggests only the form that such consideration should take Given

the patient s total clinical presentation what is the likelihood of each relevant outcome if only medical therapy is employed What is the likelihood if bypass surgery is undertaken?

This latter question is particularly difficult since reported series are often not comparable and since there is considerable variation among these series[6,7] The truly relevant data would bear on the prognosis of the *particular* patient at the particular institution where he is to be managed and where it is proposed that surgery be performed If that surgery is to be performed at a community hospital averaging just fifty bypass procedures annually are data that refer to a hospital performing over a thousand procedures each year relevant?

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The third problem encountered in this approach centers about the question of utilities—whose values should be used and how can they be obtained? Setting aside limitations imposed by resource constraints and over all societal cost the most logical source of these values is the patient himself since only he can express the burden which his angina represents and only he can evaluate the burden which early death would create

Since the proposed model is quite simple only ten outcomes need be considered Therefore one can examine the patient s attitudes toward each of the potential outcomes explicitly The method described in the *Annals* proposes the *lottery* technique for debriefing the patient of his values The essence of that technique is to offer the patient a series of simple choices between one hypothetically guaranteed outcome and a gamble between two more extreme alternatives By altering the odds of that gamble the physician can find a point where the patient is indifferent between the guaranteed outcome and the gamble The odds of the gamble at that point of indifference can be used to establish the utility of the guaranteed outcome In my experience such debriefing can be comfortably accomplished in less than one hour and most patients can understand and respond to the hypothetical alternatives

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Hospital B For example, there is a 0 25 probability of Pain relief but fatal MI" (death within five years) if surgery is performed at *Hospital A* Since Mr Jones assigns a utility of 60 to this outcome the contribution of this outcome to the expected value of surgery for Mr Jones at *Hospital A* is 0 25 × 60 or 15 In contrast Mr Smith assigns a utility of 85 to this outcome and the contribution of this outcome to the expected value of surgery is 0 25 × 85, or 21, for him Making similar calculations for each potential outcome of surgery and summing, one can see that at *Hospital A* the expected value for Mr Jones is 60 whereas the expected value for Mr Smith is 72

One would expect the rational patient to elect the therapy which offers him the higher expected value Thus, Mr Jones would likely choose medical therapy at *Hospital A* but surgical therapy at *Hospital B* Similarly, Mr Smith should also opt for medical therapy at *Hospital A* but should consider the optimal choice at *Hospital B* to be a toss up One can see from *this example that given identical anatomy and* clinical presentation, the correct decision varies from patient to patient and from hospital to hospital

This analysis raises several serious questions about the medical care that might be offered to these patients Is it reasonable for patients who present to *Hospital A* to decline surgical therapy? Should they be informed about the better results at *Hospital B* and be offered surgery there? Indeed should any patient be offered bypass surgery at *Hospital A* if he might have a better result at *Hospital B?* Certainly additional factors such as geographic constraints convenience and availability enter into such decisions

These complex questions cannot be decided here and probably should not be decided by individual physicians These issues must eventually be addressed by both organized medicine and society but until that time the method of clinical decision making proposed here should allow the choice to be optimized for the individual patient facing the resources of a specific hospital

Certainly the use of this technique will create problems for both the patient and the physician The patient will be forced to explicitly examine his innermost feelings about life and death The physician will have to take more time in order to help the patient in that examination and will be forced to deal with his own uncertainties about prognosis in an explicit manner These problems must be faced by the physician if he is to provide his patients a basis for truly informed consent

This approach will, of course not be appropriate for all patients facing the possibility of bypass surgery Some patients may not wish to bear the burden of participation in the decision making process, while others may have difficulty with the concepts involved Although the physician must rely on his perception of the patient s attitudes in such circumstances this approach should still assist the clinician as he considers the uncertainties about prognosis

The use of decision analysis is not limited to choices involving surgical therapy Rather, it is generally applicable to those therapeutic decisions which must be made despite uncertainties in *data about prognosis and to those* decisions which might be strongly influenced by the patient s attitudes In such situations explicit decision making should lead to better decisions—decisions *tailored to the available resources,* decisions consistent with the patient s desires and attitudes, and decisions reflecting the true skill of the physician

REFERENCES

1 Pauker S G Coronary artery surgery the use of decision analysis Ann Intern Med **85** 8 1976
2 Raiffa H Decision Analysis Reading Mass 1968 Addison Wesley
3 Schwartz W B Gorry G A Kassirer J P and Essig A Decision analysis and clinical judgment Am J Med **55** 459 1973
4 Kassirer J P The principles of clinical decision making an introduction to decision *analysis* Yale J Biol Med **49** 149 1976
5 Humphries J O Decision analysis and coronary surgery Ann Intern Med **85** 123 1976
6 Dunkman W B Perloff J K Kastor J A et al Medical perspective in coronary artery surgery—a caveat Ann Intern Med **81** 817 1974
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Left ventricular performance and graft patency after coronary artery–saphenous vein bypass surgery Early and late follow-up

Carl S Apstein M D
Susan A Kline M D
David C Levin M D
Harold A Baltaxe M D
Thomas Killip M D
New York N Y

Coronary artery–saphenous vein bypass graft surgery is currently being advocated as a form of treatment for coronary artery disease but the long term effects of this operation on ventricular function have not been clearly established[1,2] Early postoperative improvement has been reported in selected patients with acute myocardial ischemia Improved function in the early postoperative period implies the preoperative presence of ischemic and depressed but viable myocardial tissue Patients with impaired left ventricular performance due to chronic stable coronary artery disease have not generally demonstrated a sustained improvement in postoperative ventricular function although early postoperative ventricular function improvement in this group of patients has also been reported

The patency of the bypass coronary grafts and of the native coronary circulation is an important determinant of postoperative myocardial function Rapid progression from partial to complete occlusion in the proximal segments of grafted coronary arteries and progressive intimal fibrous proliferation of the vein grafts have been reported Postoperative graft patency is related to the rate of flow through the graft at the time of surgery but this measurement can only be made after surgery is performed

Preoperative measurements which predicted the risk of postoperative graft occlusion and ventricular performance would be useful in evaluating patients for surgery In order to evaluate long term postoperative left ventricular performance and graft patency and to develop predictive guidelines in these two areas we have reviewed the pre and postoperative angiographic studies in 26 patients who underwent coronary artery bypass graft surgery

Methods

Patient material The angiograms of 118 patients who underwent coronary artery–saphenous vein bypass graft surgery at the New York Hospital-Cornell Medical Center during a consecutive 24 month period were reviewed The criteria for inclusion in this study consisted of technically adequate pre and postoperative left ventriculograms preoperative coronary arteriograms and postoperative venograms of the bypass grafts Patients were excluded if an aneurysectomy was done a the time of coronary artery surgery Twenty six patients (22 per cent) met these criteria and form the basis of this report Eighteen patients had a single postoperative study eight patients underwent both early and late follow up angiography Thus a total of 34 postoperative studies were performed in 26 patients Twenty five patients were male the average age was 51 years

The indication for surgery in each case was the presence of angina pectoris which was disabling enough to warrant surgery in the judgment of the

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REFERENCES

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Table II Left ventricular function at early follow up

	EF	$\bar{V}$ (circ/sec)	LVEDP (mm Hg)	Heart rate (beats/min)	LV systolic press (mm. Hg)
All patients (n = 19)					
Preoperative	0 50 ± 0 04	1.39 ± 0 11	20 ± 2	77 ± 3	138 ± 4
Postoperative	0 54 ± 0 04	1 43 ± 0 19	14 ± 1	94 ± 4	121 ± 4
Patients with moderately abnormal preoperative LV function (EF 0 30 – 0 60 n = 7)					
Preoperative	0 38 ± 0 04	1 05 ± 0 15	20 ± 3	78 ± 3	132 ± 7
Postoperative	0 47 ± 0 06	1 32 ± 0 14	16 ± 2	93 ± 8	119 ± 4

$p < 0.01$ $p < 0.05$

measured by an atherosclerotic score obtained by adding the values ascribed to each stenotic lesion in a major coronary artery Scoring of lesions was done as follows total occlusion = 4 75 to 99 per cent stenosis = 3 50 to 75 per cent stenosis = 2 less than 50 per cent stenosis = 1 no lesions = 0

After surgery all patients were advised to undergo follow up catheterization regardless of their symptomatology The decision to have such a study rested with the patient and his own physicians Early postoperative studies prior to discharge from the hospital were obtained in 19 patients with 38 grafts at an average postoperative interval of 14 days and ranging up to 4 months Fifteen patients had a late follow up study between 4 months and 1 year after surgery (mean = 9 months) The patients who underwent a follow up study are thus selected in the sense that they represent the survivors of the operation who consented to restudy

At the time these data were collected 27 patients with adequate preoperative studies were long term survivors (> 4 months after operation) In order to ascertain whether the late restudy group was an unbiased sample of this late postoperative survivor population preoperative measurements were compared for the 15 patients who were restudied at late follow up and those 12 who were long term survivors and thus candidates for restudy but who did not consent These groups are compared in Table I In terms of preoperative left ventricular function and severity of coronary artery disease the patients who returned for late follow up study were a representative sample of all the patients operated upon who survived for at least 4 months

Statistical analysis of the data reported herein was performed with the paired or unpaired Student s t test, as appropriate for hemodynamic data To analyze the significance of the different risks of graft occlusion the value of p was calculated from a 2 by 2 contingency table with the Fisher exact probability test Data are reported as the mean ± standard error of the mean (S E M)

Results

Extent of atherosclerosis All patients in this series had significant coronary artery disease demonstrated by coronary angiography The mean atherosclertic score for the 26 patients was 6 0 Ejection fraction was inversely related to the atherosclerotic index the 16 patients with an ejection fraction less than 0.50 had an atherosclerotic score of 7 0 ± 0 5 the 10 patients with an ejection fraction greater than 0 50 had an atherosclerotic score of 5 4 ± 0 6 ($p < 0.05$ unpaired t test)

Early postoperative studies

Ventricular function Left ventricular function as assessed by ejection fraction and mean rate of circumferential shortening was unchanged at the time of the 14 day follow up study in the group of 19 patients considered as a whole (Table II) However the postoperative LVEDP significantly decreased heart rate increased and peak left ventricular systolic pressure decreased Since left ventricular peak systolic pressure was significantly lower and heart rate was significantly higher at this time the observed decline in LVEDP may not represent a primary improvement of myocardial function

The group of 19 patients was separated on the basis of preoperative ejection fraction The subgroup of seven patients with a moderately impaired preoperative ejection fraction (0 30 to 0 60) had an increase in ejection fraction at early

Table I Preoperative values Late vs no late follow up study

	Late study (n = 15)	*No late study (n = 12)*	*P**
Ejection fraction	0 62 ± 0 05	0 58 ± 0 04	N S
Mean rate of circumferential shortening	1 29 ± 0 11	1 39 ± 0 14	N S
Atherosclerotic score	6 5 ± 1 8	5 7 ± 0 8	N S

*Unpaired Student s t test

patient and his physicians All patients had a "stable clinical level of angina, there were no cases of 'crescendo' or unstable angina,' or the intermediate coronary syndrome' Fifty one grafts, or an average of two per patient, were implanted and subsequently studied

Angiographic studies The angiographic studies evaluated the extent of preoperative coronary artery atherosclerosis, pre and postoperative left ventricular function and postoperative graft patency Three patients also had postoperative coronary arteriography Left ventricular catheterization was performed from the right femoral artery Pressure measurements were recorded prior to the injection of contrast material Preoperative coronary arteriography was performed with the Judkins technique Selective saphenous vein graft angiograms were performed and examined for graft occlusion at the time of each postoperative study If the grafts were patent, the flow pattern in the anastomosed coronary artery was characterized as *unidirectional* if contrast material flowed only antegrade into the artery, or *bidirectional* if there was also retrograde flow into the proximal segment of the grafted artery Lack of bidirectional flow in the grafted artery was interpreted as indicating that an occlusion in the proximal segment of the artery had occurred In one case of unidirectional antegrade flow in the grafted artery, coronary arteriography demonstrated occlusion of the proximal arterial segment Coronary arteriography was not performed in the other instances where the proximal arterial segment failed to fill from the injection into the graft However, lack of retrograde flow in the proximal segment of the grafted artery during injection into the venous graft has generally correlated with occlusion in the proximal segment of the native coronary artery,[16] although the precise location of the site of occlusion cannot be delineated solely by graft angiography

After coronary arteriography, the patients were allowed to recover for approximately 30 minutes while the coronary films were developed and reviewed after which time a left ventriculogram was performed and the ejection fraction was determined In those patients where the left ventricular end diastolic pressure (LVEDP) increased after coronary arteriography the ventriculogram was delayed until the LVEDP returned to the pre-coronary arteriogram value The LVEDP usually returned to the control value within 30 minutes This protocol should have minimized any influence upon our ventriculographic data of the effect of the contrast material injected during coronary artery or vein graft angiography[21 23] The reproducibility of the ejection fraction (EF) measurement has been assessed by comparing angiograms performed 90 minutes before and 30 minutes after coronary angiography[4], there was no significant difference between the two EF measurements Thus our assessment of ventricular function via ventriculography performed 30 minutes after coronary arteriography should be free from the effects of the arteriography The preoperative, early, and late follow up studies were all performed with the same protocol

Analysis of ventricular function was performed by calculating the EF [7] and the mean rate of circumferential shortening ($\bar{V}_{CF}$) on normal sinus beats occurring at least two beats after premature beats The EF obtained from the right anterior oblique ventriculograms were converted to biplane values [8] The EF was derived from the formula EF = (EDV – ESV)/EDV where EDV and ESV represent the end diastolic and end systolic volumes respectively The $\bar{V}_{CF}$ in circumferences per second was derived from the formula [8] $\bar{V}_{CF}$ = (EDC – ESC)/EDC/ET where EDC and ESC represent the end diastolic and end systolic circumferences respectively and ET represents the ejection time in seconds The EF and $\bar{V}_{CF}$ were determined in duplicate and independently by two of the authors (C S A and S A K) for each patient the values determined in this manner were in close agreement and the average is reported herein Thus observer to observer error [7] was minimized

The extent of coronary artery disease was

Table II Left ventricular function at early follow up

	EF	$\bar{V}$ *(cir/sec)*	*LVEDP (mm Hg)*	*Heart rate (beats/min)*	*LV systolic press (mm Hg)*
All patients (n = 19)					
Preoperative	0.50 ± 0.04	1.32 ± 0.11	20 ± 2	77 ± 3	138 ± 4
Postoperative	0.54 ± 0.04	1.43 ± 0.12	14 ± 1	94 ± 4	121 ± 4
Patients with moderately abnormal preoperative LV function (EF 0.30 – 0.60 n = 7)					
Preoperative	0.38 ± 0.04	1.05 ± 0.15	20 ± 3	78 ± 3	132 ± 7
Postoperative	0.47 ± 0.06	1.22 ± 0.14	16 ± 2	93 ± 8	119 ± 4

$p < 0.01$ $p < 0.05$

measured by an atherosclerotic score obtained by adding the values ascribed to each stenotic lesion in a major coronary artery Scoring of lesions was done as follows total occlusion = 4 75 to 99 per cent stenosis = 3 50 to 75 per cent stenosis = 2 less than 50 per cent stenosis = 1 no lesions = 0

After surgery all patients were advised to undergo follow up catheterization regardless of their symptomatology The decision to have such a study rested with the patient and his own physicians Early postoperative studies prior to discharge from the hospital were obtained in 19 patients with 38 grafts at an average postoperative interval of 14 days and ranging up to 4 months Fifteen patients had a late follow up study between 4 months and 1 year after surgery (mean = 9 months) The patients who underwent a follow up study are thus selected in the sense that they represent the survivors of the operation who consented to restudy

At the time these data were collected 27 patients with adequate preoperative studies were long term survivors (> 4 months after operation) In order to ascertain whether the late restudy group was an unbiased sample of this late postoperative survivor population preoperative measurements were compared for the 15 patients who were restudied at late follow up and those 12 who were long term survivors and thus candidates for restudy but who did not consent These groups are compared in Table I In terms of preoperative left ventricular function and severity of coronary artery disease the patients who returned for late follow up study were a representative sample of all the patients operated upon who survived for at least 4 months

Statistical analysis of the data reported herein was performed with the paired or unpaired Student s t test as appropriate for hemodynamic data To analyze the significance of the different risks of graft occlusion the value of p was calculated from a 2 by 2 contingency table with the Fisher exact probability test Data are reported as the mean ± standard error of the mean (S E M)

Results

Extent of atherosclerosis All patients in this series had significant coronary artery disease demonstrated by coronary angiography The mean atherosclertic score for the 26 patients was 6 0 Ejection fraction was inversely related to the atherosclerotic index the 16 patients with an ejection fraction less than 0 50 had an atherosclerotic score of 7 0 ± 0 5 the 10 patients with an ejection fraction greater than 0 50 had an atherosclerotic score of 5 4 ± 0 6 (p < 0 05 unpaired t test)

Early postoperative studies

Ventricular function Left ventricular function as assessed by ejection fraction and mean rate of circumferential shortening was unchanged at the time of the 14 day follow up study in the group of 19 patients considered as a whole (Table II) However the postoperative LVEDP significantly decreased heart rate increased and peak left ventricular systolic pressure decreased Since left ventricular peak systolic pressure was significantly lower and heart rate was significantly higher at this time the observed decline in LVEDP may not represent a primary improvement of myocardial function

The group of 19 patients was separated on the basis of preoperative ejection fraction The subgroup of seven patients with a moderately impaired preoperative ejection fraction (0.30 to 0 60) had an increase in ejection fraction at early

Table III Postoperative graft patency

	No of patients			No of grafts		
	Studied	All grafts patent	One or more graft occlusions	Implanted	Patent	Occluded (%)
Early follow up (<4 mo)						
Preoperative EF > 0 60	9	9	0 *	16	16	0 (0%)
Preoperative EF < 0 60	10	5	5	22	16	6 (27%)
Total	19	14	5	38	32	6 (16%)
Late follow up (>4 mo)						
Preoperative EF > 0 60	11	8	3**	21	17	4 (19%)
Preoperative EF < 0 60	4	0	4	10	5	5 (50%)
Total	15	8	7	31	22	9 (29%)
Combined early and late follow up						
Preoperative EF > 0 60	16	13	3	29	25	4 (14%)
Preoperative EF < 0 60	10	3	7**	22	14	8 (37%)
Total	26	16	10	51	33	12 (24%)

Each patient counted singly with data based on latest study
$P < 0.05$ for risk of graft occlusion Fisher exact test two tailed

follow up and a trend toward an increased $\bar{V}_{cf}$ which was not statistically significant The increase in ejection fraction at a lower end diastolic pressure may indicate a slight improvement in ventricular function in these patients but could also be due to the lower postoperative afterload (LV systolic pressure) and higher heart rate Two of the seven patients with an improved ejection fraction postoperatively had been digitalized between the pre and postoperative studies Thus the finding of early postoperative improvement in the ejection fraction must be interpreted cautiously

The subgroup of nine patients who had a normal preoperative ejection fraction (greater than 0 60) had no significant change in ejection fraction at early follow up Three patients had a preoperative ejection fraction less than 0 20, there was no significant change at early follow up

Graft patency Thirty eight grafts in 19 patients were studied at early follow up (Table III) Sixteen per cent (6 of 38) of the grafts were occluded Eighty four per cent (32 of 38) of the grafts were patent and 30 of the patent grafts had bidirectional flow of contrast material into the coronary artery distal to the site of anastomosis In two cases the anastomosed coronary artery exhibited only antegrade flow of contrast material from the venous graft indicating probable occlusion in the proximal segment of the grafted native coronary artery

Graft patency in the early postoperative period was related to the preoperative ejection fraction The risk of graft occlusion at early follow up was zero if the preoperative EF had been greater than 0 60 but there was a 27 per cent risk of occlusion for each implanted graft when the preoperative ejection fraction was less than 0 60 All patients with a preoperative EF greater than 0 60 remained free of any graft occlusion, while 50 per cent of those patients with a preoperative EF of less than 0 60 suffered at least one graft occlusion

Late post operative studies Thirty one grafts were studied in 15 patients at an average postoperative interval of nine months (Table III) and ventricular function was studied in fourteen of the fifteen patients (Fig 1)

Graft patency Nine of the grafts were occluded (29 per cent) Twenty two grafts (71 per cent) were patent and 19 showed bidirectional flow in the anastomotic coronary artery Three were patent, but filled only the distal portion of the grafted coronary artery indicating probable occlusion in the proximal segment of the grafted coronary artery As with the early postoperative studies graft patency at 9 months follow up was associated with a normal preoperative ejection fraction

The risk of graft occlusion when the early and late follow up studies are considered together, was much higher for those patients with abnormal preoperative ventricular function (Table III) Over all 51 grafts were restudied in 26 patients In the 16 patients with a preoperative

EF greater than 0.60 four of 29 grafts (14 per cent) were occluded in the 10 patients with a preoperative EF less than 0.60 the risk of graft occlusion was 37 per cent (eight of 22 grafts). Graft occlusions occurred in seven of 10 patients who had a preoperative EF less than 0.60 but in only three of 16 patients who had a preoperative EF greater than 0.60.

Ventricular function. The EF and $\bar{V}_{CF}$ were significantly reduced from the preoperative values in the late postoperative period in the group of patients considered as a whole (Fig. 1). For the total group of late follow up studies the EF decreased from 0.62 ± 0.05 to 0.54 ± 0.05 ($p < 0.01$ paired t test) and the $\bar{V}_{CF}$ decreased from 1.29 ± 0.11 to 1.11 ± 0.12 circumferences per second ($p < 0.02$ paired t test). The left ventricular systolic pressure decreased from 130 $\pm$ 6 mm Hg preoperative to 114 $\pm$ 5 mm Hg postoperative ($p < 0.01$ paired t test). There was no significant change in heart rate (79 $\pm$ 3 preoperative vs 78 $\pm$ 2 mm Hg postoperative). The significant decrease in EF and $\bar{V}_{CF}$ at constant heart rate and end diastolic pressure but with reduced afterload (peak LV systolic pressure) indicates a reduction of ventricular function in the late postoperative period.

When the patients were divided into subgroups on the basis of graft patency and flow pattern in the grafted coronary artery (Fig. 1) it was found that the subgroup without graft occlusions and with bidirectional flow into the grafted artery had maintained left ventricular performance at their normal preoperative level. The subgroup with occluded grafts or unidirectional antegrade flow in the grafted artery showed a significant decrease in left ventricular EF from 0.59 ± 0.07 to 0.49 ± 0.07 ($p < 0.01$ paired t test) and in $\bar{V}_{CF}$ from 1.21 ± 0.14 to 1.01 ± 0.15 circumferences per second ($p < 0.05$ paired t test).

Sequential studies in the same patients. Eight patients had follow up studies during both the early and late postoperative periods (Table IV). This small group showed a trend which was similar to the entire study group no change in ventricular function at early follow up with a decrease in the late follow up period. Six of the eight patients had occlusions of at least one vein graft or of a proximal coronary artery segment at the late postoperative study. These six patients had a decrease from a preoperative EF of 0.58 ± 0.09 to 0.45 ± 0.80 ($p < 0.05$ paired t

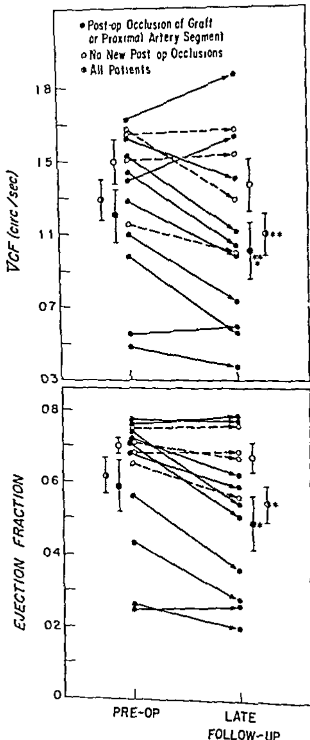


Fig. 1. Left ventricular function preoperatively and at late follow up. Connecting lines indicate pre and postoperative values for each patient. The mean values $\pm$ S.E.M. are indicated for each group. Statistical significance between the pre- and postoperative studies is indicated by for $p < 0.01$ for $p < 0.02$ and for $p < 0.05$ (paired Student's t test).

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The risk of graft occlusion, when the early and late follow up studies are considered together, was much higher for those patients with abnormal preoperative ventricular function (Table III) Over all 51 grafts were restudied in 26 patients In the 16 patients with a preoperative

free of occlusion and who demonstrated bidirectional flow in the grafted coronary artery were without a decrease in ventricular performance (Fig 1)

Early follow up In the early follow up period the postoperative ejection fraction was not closely correlated with graft patency Three patients who had suffered graft occlusion also had an improved ejection fraction The six graft occlusions which occurred in the early follow up period took place in that subgroup of patients who demonstrated improved postoperative left ventricular performance i.e the subgroup with an abnormal preoperative ejection fraction The five patients with one or more graft occlusions at early follow up did not demonstrate a significant decrease in ejection fraction (Fig 2)

In addition to the direct effects of the coronary artery surgery a number of nonsurgical factors may have affected early postoperative ventricular performance Two of the seven patients with abnormal preoperative ventricular function had been digitalized between the pre and postoperative studies the postoperative hospital environment with its restriction in physical activity and regulated medical management of drugs and diet may have been a factor in the early postoperative improvement in ventricular function in the group as a whole The stress of surgery has been shown to increase catecholamine excretion and may be an important determinant of ventricular function in the early postoperative period [7, 10] The higher mean heart rate in our early postoperative studies is consistent with this hypothesis Furthermore the increased heart rate and decreased afterload observed in the early postoperative period would tend to increase the ejection fraction and therefore the observed increase in EF cannot be attributed entirely to a primary improvement in ventricular function Since left ventricular end diastolic pressure decreased in the early postoperative studies of those patients showing an improvement in ejection fraction as it did in the group as a whole the early improvement in ejection fraction cannot be attributed to increased preload Rather the early postoperative decrease in end diastolic pressure probably resulted from the decreased left ventricular afterload and higher heart rate Thus nonsurgical factors may increase early postoperative ventricular function and temporarily mask any deterioration secondary to graft occlusion

Mitral regurgitation did not occur *de novo* or increase in severity in any postoperative study therefore postoperative ejection fraction was not increased on this basis

Late follow up In contrast to the early follow up studies the presence and pattern of coronary flow in the vein graft and grafted artery was an important determinant of late postoperative ventricular function (Fig 1) The 10 patients who suffered occlusions of one or more venous grafts or failed to fill the proximal segment of the native grafted coronary artery had a significant decrease in ventricular function while the four patients who had 100 per cent graft and proximal artery segment patency maintained normal ventricular function Proximal coronary artery occlusion could have important functional consequences if the involved proximal segment supplied a significant number of secondary arterial branches to the left ventricle In such a case occlusion of this segment could lead to a significant loss in regional myocardial perfusion despite graft patency and good flow in the distal coronary artery segment [1, 16] A decline in ventricular performance at late follow up could not be attributed to any drugs with a negative inotropic effect taken *de novo* by any of the patients in the late postoperative period

The potential for myocardial revascularization to improve ventricular function would appear to be limited on theoretical grounds It would seem apparent that the mere presence of a new supply of oxygen could not convert scar tissue into functioning sarcomeres however depression of muscle function due to oxygen lack could theoretically be reversed if the ischemia were corrected before myocardial necrosis occurred A significant early postoperative improvement in left ventricular contractility has been reported in the immediate postoperative period in a selected group of patients with a recent acute increase in the severity of their anginal syndrome these patients presumably had ischemically depressed tissue which had not yet become irreversibly damaged

In contrast most studies of patients with stable coronary artery disease without a recent increase in anginal symptomatology have not shown a consistent improvement of abnormal ventricular function [2] In the early postoperative period the ejection fraction has been reported to increase [3, 1] as we have reported for a selected subgroup in this

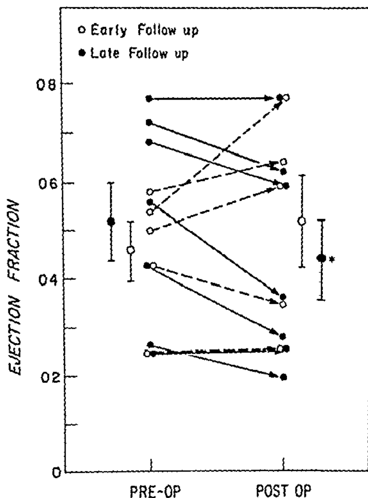


Fig 2 Effect of graft occlusion on ejection fraction at early and late follow up studies All patients who suffered postoperative graft occlusion are shown The mean values ± S E M are indicated for each group Statistical significance is indicated by * for $p < 0.05$ (paired Student's t test)

Table IV Sequential studies of ventricular function in eight patients

	Preoperative	*Early postoperative*	*Late postoperative*
EF	0.61 ± 0.07	0.61 ± 0.07	0.52 ± 0.07
$\bar{V}_{cf}$	1.27 ± 0.13	1.32 ± 0.16	1.11 ± 0.18

$p < 0.05$ $p = 0.1-0.2$ (paired Student's t test)

test) at late follow up There was no significant change in heart rate LVEDP or peak systolic pressure between the preoperative and late postoperative studies in these patients so that the decrease in EF probably represents a true decline in ventricular function

Comparison of the effect of graft occlusion at early and late follow up In the early postoperative studies five patients had one or more occluded bypass grafts there was no significant difference between the pre and early postoperative EF in this group of patients In the late postoperative studies, seven patients had one or more occluded grafts, in contrast to the early postoperative studies, these seven cases demonstrated a significant reduction in EF (Fig 2) Thus the detrimental effect of graft occlusion may not become manifest immediately, but becomes apparent later in the postoperative course

Discussion

The results of this study indicate (1) a correlation between a diminished preoperative left ventricular ejection fraction and an increased risk of postoperative graft occlusion and (2) a failure of coronary artery-saphenous vein bypass surgery to effect a long term improvement in postoperative left ventricular function despite improved function in the early postoperative period in a selected subgroup

Graft patency Our data indicate that patients with impaired preoperative ventricular function as reflected by an ejection fraction of less than 0.60 had a significantly greater risk of postoperative graft occlusion (Table III) This observation has not been previously reported The site of the vein graft (right coronary left anterior descending or circumflex) did not significantly influence the risk of graft occlusion a finding in accord with others [15] The mechanism by which impaired left ventricular function led to a higher risk of graft occlusion was not studied but it is likely that patients with abnormal preoperative ejection fractions had more severe distal coronary artery disease which could have directly reduced graft flow in the anastomosed vessel

Left ventricular performance Left ventricular ejection fraction and mean rate of circumferential shortening were not significantly changed from their preoperative values at the time of early postoperative study in the total group of patients studied However a small but significant improvement in the ejection fraction and a similar trend in the mean rate of circumferential shortening was noted in a selected subgroup of patients who had demonstrated a moderate reduction in preoperative left ventricular function (Table II) Late follow up studies showed a significant decline in both left ventricular ejection fraction and the mean rate of circumferential shortening compared to values obtained preoperatively in the total group studied At late follow up only a minority of patients who had remained

19 Kern W H Dermer G B, and Lindesmith G G The intimal proliferation in aortic coronary saphenous vein grafts Am Heart J 84 771 1972
20 Walker S A Friedberg H D Flemma R J and Johnson W D Determinants of angiographic patency of aortocoronary vein bypass grafts Circulation 45(Suppl. I) 86 1972
21 Friesinger G C Schaffer J Criley J M Gaertner R A and Ross R S Hemodynamic consequences of the injection of radiopaque material, Circulation 31 730 196
22 Rahimtoola M B Duffy J P and Swan H J C Ventricular performance after angiocardiography Circulation 35 70 1967
23 Cohn P F Horn H R Teichholz L E Kreulen T H Herman M V and Gorlin R Effects of angiographic contrast medium on left ventricular function in coronary artery disease Comparison with static and dynamic exercise Am J Cardiol. 32 31 1973
24 Cohn P F Levine J A Bergeron G A and Gorlin R. Reproducibility of the angiographic left ventricular ejection fraction in patients with coronary artery disease Am Heart J 88 713 1974
25 Sandler H and Dodge H T The use of single plane angiocardiograms for the calculation of left ventricular volume in man Am Heart J 75 325 1968
26 Kennedy J W Trenholme S E and Kasser I S Left ventricular volume and mass from single plane cine angiocardiogram A comparison of antero posterior and right anterior oblique methods Am Heart J 80 343 1970
27 Chatterjee K., Sacoor H Sutton G C and Miller G A H Assessment of left ventricular function by single plane cine angiographic volume analysis Br Heart J 33 565 1971
28 Karliner J S Gault J H Eckberg D Mullins, C B and Ross J Jr Mean velocity of fiber shortening A simplified measure of left ventricular myocardial contractility Circulation 44 323 1971
29 Bailey N T J Statistical methods in biology New York 1959 John Wiley & Sons Inc pp 61-64
30 Rees C., Bristow J D Kremkau E L Green G S Herr R H Griswold H F and Starr A Influence of aortocoronary bypass surgery on left ventricular performance N Engl J Med 284 1116 1971
31 Bolooki, H., Rubinson R M., Michie D D and Jude J R Assessment of myocardial contractility after coronary bypass grafts J Thorac Cardiovasc. Surg 62 543 1971

paper However longer term follow up studies[1] have shown no significant improvement of ventricular function in patients with all grafts patent, and deterioration of ventricular function with graft occlusion, results which are in agreement with our data

The long term effect of bypass graft surgery upon left ventricular ejection fraction in patients with chronic stable angina and left ventricular dysfunction is not encouraging At late follow up in our series all four patients with an abnormal preoperative left ventricular ejection fraction had suffered graft occlusion and this group had a further decline in ventricular function Of the patients with normal preoperative left ventricular function graft or proximal coronary artery occlusions occurred in the majority (six of 11 patients) and ventricular function became abnormal post operatively No patient in the 9 month follow up period had a significant improvement in an abnormal preoperative ejection fraction Thus coronary bypass should not be performed in an attempt to improve ventricular function in the patient who has a stable chronic level of anginal symptomatology

Summary

Left ventricular performance and graft patency were studied postoperatively at 2 weeks in 19 patients, and at 9 months in 15 patients At early follow up left ventricular ejection fraction and mean rate of circumferential shortening were unchanged for the group as a whole but were slightly improved in patients who had had a moderately abnormal preoperative ejection fraction of 0 30 to 0 60 At late follow up 10 of 14 patients had occluded at least one graft or the proximal segment of the grafted coronary artery and had an associated decrease in ventricular function The risk of graft occlusion was greater if the preoperative ejection fraction was decreased seven of 10 patients with a preoperative EF of less than 0 60 suffered one or more graft occlusions but only three of 16 patients with a preoperative EF greater than 0 60 had a postoperative graft occlusion ($p < 0.05$) The results suggest that bypass graft surgery is not generally indicated as a measure to improve ventricular function in patients with ischemic heart disease

REFERENCES

1 Manley H and Johnson D Effects of surgery on angina (pre and post infarction) and myocardial function (failure) Circulation **46** 1208 1972

2 Editorial Coronary bypass surgery Lancet 1 13, 1973

3 Sustaita H Chatterjee K Matloff J M Marty A T Swan H J C and Fields J Emergency bypass surgery in impending and complicated acute myocardial infarction Arch Surg **105** 30 1972

4 Chatterjee K Swan H J C Parmley W W Sustaita H Marcus H and Matloff J Depression of left ventricular function due to acute myocardial ischemia and its reversal after aortocoronary saphenous vein bypass N Engl J Med **286** 1117 1972

5 Spencer F C Green G E Tice D A Wallsh E Mills N L and Glassman E Coronary artery bypass grafts for congestive heart failure A report of experiences with 40 patients J Thorac Cardiovasc Surg **62** 529 1971

6 Kouchoukos N Doty D B Buettner L E and Kirklin J W Treatment of post infarction cardiac failure by myocardial excision and revascularization Circulation **45**(Suppl I) 72 1972

7 Hammermeister K E Kennedy J W Hamilton G W Steward D K Gould K L Lipsomb K and Murray J A The effect of vein bypass grafting on resting left ventricular function N Engl J Med **290** 186 1974

8 Shepherd R L Itscoitz S B Glancy D L Stinson E B Reis R L Olinger G N Clark C E and Epstein S E Deterioration of myocardial function following aorto coronary bypass operation Circulation **49** 467 1974

9 Gott V L Outlook for patients after coronary artery revascularization Am J Cardiol **33** 431 1974

10 Bourassa M Left ventricular performance following direct myocardial revascularization (Editorial) Circulation **48** 915 1973

11 Deal P Elliott L P Bartley T D Wheat M W Jr and Ramsey H W Quantitative left ventriculography in the immediate postoperative period after aorto coronary bypass J Thorac Cardiovasc Surg **66** 1 1973

12 Arbogast R Solignac A and Bourassa M Influence of aortocoronary saphenous vein bypass surgery on left ventricular volumes and ejection fraction Comparison before and one year after surgery in 51 patients Am J Med **54** 290 1973

13 Chatterjee K Swan H J C Parmley W W Sustaita H Marcus H S and Matloff J Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease with and without previous myocardial infarction Circulation **47** 276 1973

14 Bolooki H Mallon S Ghahramani A Sommer L Vargas A Salvin D and Kaiser G A Objective assessment of the effects of aorto coronary bypass operation on cardiac function J Thorac Cardiovasc Surg **66** 916 1973

15 Levine J A Bechtel D J Gorlin R Cohn P F Herman M V Cohn L H and Collins J J Jr Coronary artery anatomy before and after direct revascularization surgery Clinical and cinearteriographic studies in 67 selected patients AM HEART J **89** 561 1975

16 Griffith L S C Achuff S Conti R Humphries J O Brawley R K Gott V L and Ross R S Changes in intrinsic coronary circulation and segmental ventricular motion after saphenous vein coronary bypass graft surgery N Engl J Med **288** 589 1973

17 Aldridge H F and Trimble A S Progression of proximal coronary artery lesions to total occlusion after aorta coronary saphenous vein bypass grafting J Thorac Cardiovasc Surg **62** 7 1971

18 Vlodaver A and Edwards J E Pathologic changes in aortic coronary arterial saphenous vein grafts Circulation **44** 719 1971

19 Kern W H Dermer G B and Lindesmith G G The intimal proliferation in aortic coronary saphenous vein grafts Am Heart J 84 771 1972
20 Walker S A Friedberg H D Flemma R J and Johnson W D Determinants of angiographic patency of aortocoronary vein bypass grafts Circulation 45(Suppl I) 86 1972
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22 Rahimtoola M B Duffy J P and Swan H J C Ventricular performance after angiocardiography Circulation 35 0 1967
23 Cohn P F Horn H R Teichholz L E Kreulen T H Herman M V and Gorlin R Effects of angiographic contrast medium on left ventricular function in coronary artery disease Comparison with static and dynamic exercise, Am J Cardiol 32 31 1973
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26 Kennedy J W Treeholme S E and Kasser I S Left ventricular volume and mass from single plane cine angiocardiogram A comparison of antero-posterior and right anterior oblique methods Am Heart J 80 343 1970
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29 Bailey N T J Statistical methods in biology New York 1959 John Wiley & Sons, Inc, pp 61-64
30 Rees C Bristow J D Kremkau E L Green G S Herr R H Griswold H E and Starr A Influence of aortocoronary bypass surgery on left ventricular performance N Engl J Med 284 1116 1971
31 Bolooki H Rubinson R M Michie D D, and Jude J R Assessment of myocardial contractility after coronary bypass grafts J Thorac Cardiovasc Surg 62 543 1971

paper However longer term follow up studies[1] have shown no significant improvement of ventricular function in patients with all grafts patent and deterioration of ventricular function with graft occlusion results which are in agreement with our data

The long term effect of bypass graft surgery upon left ventricular ejection fraction in patients with chronic stable angina and left ventricular dysfunction is not encouraging At late follow up in our series, all four patients with an abnormal preoperative left ventricular ejection fraction had suffered graft occlusion and this group had a further decline in ventricular function Of the patients with normal preoperative left ventricular function graft or proximal coronary artery occlusions occurred in the majority (six of 11 patients) and ventricular function became abnormal post operatively No patient in the 9 month follow up period had a significant improvement in an abnormal preoperative ejection fraction Thus coronary bypass should not be performed in an attempt to improve ventricular function in the patient who has a stable chronic level of anginal symptomatology

Summary

Left ventricular performance and graft patency were studied postoperatively at 2 weeks in 19 patients, and at 9 months in 15 patients At early follow up left ventricular ejection fraction and mean rate of circumferential shortening were unchanged for the group as a whole but were slightly improved in patients who had had a moderately abnormal preoperative ejection fraction of 0 30 to 0 60 At late follow up 10 of 14 patients had occluded at least one graft or the proximal segment of the grafted coronary artery and had an associated decrease in ventricular function The risk of graft occlusion was greater if the preoperative ejection fraction was decreased seven of 10 patients with a preoperative EF of less than 0 60 suffered one or more graft occlusions but only three of 16 patients with a preoperative EF greater than 0 60 had a postoperative graft occlusion ($p < 0.05$) The results suggest that bypass graft surgery is not generally indicated as a measure to improve ventricular function in patients with ischemic heart disease

REFERENCES

1 Manley H and Johnson D Effects of surgery on angina (pre and post infarction) and myocardial function (failure) Circulation 46 1208 1972
2 Editorial Coronary bypass surgery Lancet 1 137 1973
3 Sustaita H Chatterjee K Matloff J M Marty A T Swan H J C and Fields J Emergency bypass surgery in impending and complicated acute myocardial infarction Arch Surg 105 30 1972
4 Chatterjee K Swan H J C Parmley W W Sustaita H Marcus H and Matloff J Depression of left ventricular function due to acute myocardial ischemia and its reversal after aortocoronary saphenous vein bypass N Engl J Med 286 1117 1972
5 Spencer F C Green G E Tice D A Wallsh E Mills N L and Glassman E Coronary artery bypass grafts for congestive heart failure A report of experiences with 40 patients J Thorac Cardiovasc Surg 62 529 1971
6 Kouchoukos N Doty D B Buettner L E and Kirklin J W Treatment of post infarction cardiac failure by myocardial excision and revascularization Circulation 45(Suppl I) 72 1972
7 Hammermeister K E Kennedy J W Hamilton C W Steward D K Gould K L Lipsomb K and Murray J A The effect of vein bypass grafting on resting lef ventricular function N Engl J Med 290 186 1974
8 Shepherd R L Itscoitz S B Glancy D L Stinson E B Reis R L Olinger G N Clark C E and Epstein S E Deterioration of myocardial function following aorto coronary bypass operation Circulation 49 467 1974
9 Gott V L Outlook for patients after coronary artery revascularization Am J Cardiol 33 431 1974
10 Bourassa M Left ventricular performance following direct myocardial revascularization (Editorial) Circulation 48 915 1973
11 Deal P Elliott L P Bartley T D Wheat M W Jr and Ramsey H W Quantitative left ventriculography in the immediate postoperative period after aorto coronary bypass J Thorac Cardiovasc Surg 66 1 1973
12 Arbogast R Solignac A and Bourassa M Influence of aortocoronary saphenous vein bypass surgery on left ventricular volumes and ejection fraction Comparison before and one year after surgery in 51 patients Am J Med 54 290 1973
13 Chatterjee K Swan H J C Parmley W W Sustaita H Marcus H S and Matloff J Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease with and without previous myocardial infarction Circulation 47 276 1973
14 Bolooki H Mallon S Ghahramani A Sommer L Vargas A Salvin D and Kaiser G A Objective assessment of the effects of aorto coronary bypass operation on cardiac function J Thorac Cardiovasc Surg 66 916 1973
15 Levine J A Bechtel D J Gorlin R Cohn P F Herman M V Cohn L H and Collins J J Jr Coronary artery anatomy before and after direct revascularization surgery Clinical and cinearteriographic studies in 67 selected patients Am Heart J 89 561 1975
16 Griffith L S C Achuff S Conti R Humphries J O Brawley R K Gott V L and Ross R S Changes in intrinsic coronary circulation and segmental ventricular motion after saphenous vein coronary bypass graft surgery N Engl J Med 288 589 1973
17 Aldridge H E and Trimble A S Progression of proximal coronary artery lesions to total occlusion after aorta coronary saphenous vein bypass grafting J Thorac Cardiovasc Surg 62 7 1971
18 Vlodaver A and Edwards J E Pathologic changes in aortic coronary arterial saphenous vein grafts Circulation 44 719 1971

for at least 6 months before the attack and an ex smoker as having stopped at least 3 months before the attack Only cigarette smoking was studied

The effect of these initial factors on subsequent morbidity and on total and coronary mortality rates was examined Morbidity was defined as further nonfatal episodes of proved ACI or MI

For statistical analysis the usual chi square test for a two way contingency was used

Factors studied at follow up examination included blood pressure serum cholesterol weight and cigarette smoking status Reduced smoking was defined as less than 50 per cent of initial consumption Stopped smoking was defined as having stopped within 6 months of the attack and having remained off cigarettes for the duration of the follow up period

Relationships between change in smoking habits and subsequent morbidity and death were sought This communication does not deal with the influence of changes in the other risk factors noted at follow up The chi square test was again used except for one question where the small sample size dictated the use of Fisher s exact probability test [6]

Mode of death was recorded as sudden fresh MI with shock heart failure other cardiac causes other vascular causes or noncardiac causes

Results

Fifty eight (27 2 per cent) of the patients presented with ACI 112 (52 6 per cent) with uncomplicated MI and 43 (20 2 per cent) with complicated MI The cumulative mortality rate was 18 per cent over 5 years with an average *annual* mortality rate of 3 5 per cent and an excess of deaths (13) in the first year There were 38 deaths of which 16 (42 per cent) were due to further MI with shock or cardiac failure 18 (47 per cent) sudden one (3 per cent) due to intractable cardiac failure and three (8 per cent) noncardiac

Fifty (24 per cent) patients suffered a total of 60 further nonfatal episodes of acute CHD Of these 50 patients 40 had one and 10 had two further nonfatal attacks

Results for initial factors Serum cholesterol diastolic blood pressure and initial smoking status did not relate significantly to long term morbidity or mortality rates The death rate increased with age but the association was not significant

Table I Effect of relative weight at initial examination on CHD and over all mortality rate

Relative weight	*No of cases*	*CHD deaths* No	*CHD deaths* %	*Total deaths* No	*Total deaths* %
Normal	102	23	22.5	25	24 5
10-19% overweight	45	7	15 6	7	15 6
20-29% overweight	43	0	0	0	0
30% or more overweight	23	5	21 7	6	26 1
Total	213	35	16 4	38	17 8

Table II Effect of severity of initial attack on CHD and over all mortality rate

Severity	*No of cases*	*CHD deaths* No	*CHD deaths* %	*Total deaths* No	*Total deaths* %
ACI	58	5	8 6	6	10.3
MI uncomplicated	112	18	16 1	20	17 9
MI complicated	43	12	27.9	12	27.9
Total	213	35	16 4	38	17 8

Table III Effect of cigarette smoking status at follow up on CHD and over all mortality rate 188 initial smokers (and 2 ex smokers who resumed)

Cigarette smoking status	*No of cases*	*CHD deaths* No	*CHD deaths* %	*Total deaths* No	*Total deaths* %
Stopped	89	11	12 4	13	14 6
Reduced	42	6	14.3	6	14.3
Continued	59	17	28 8	17	28.8
Total	190	34	17 9	36	18 9

Table IV Effect of severity of initial attack on mortality rate within each category of smoking status at follow up of 188 initial cigarette smokers

	Severity				
	ACI + uncomplicated MI		*Complicated MI*		
	Stopped and reduced	*Continued*	*Stopped and reduced*	*Continued*	*Total*
No of patients	106	46	25	11	188
No died	15	9	4	7	35
Per cent died	14 1	19 6	16	63 6	18 6

Factors affecting the 5 year survival rate of men following acute coronary heart disease

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Epidemiological and clinical studies have shown that certain person attributes increase the risk of developing a first myocardial infarction (MI)[1] Less is known about the factors affecting the prognosis of men surviving their first episode of acute coronary heart disease (CHD) Identification of these factors is necessary to allow a rational approach to the management of patients with established CHD

In the present report the effect of a number of initial factors on the incidence of subsequent nonfatal and fatal coronary attacks is noted We comment also on survival and on the mode of death in patients who continued to smoke compared to those who reduced or stopped smoking

This paper follows a previous publication[2] in which patients who had an initially complicated MI or who continued to smoke heavily after infarction had a high mortality rate over 4 years The present report is based on a group comprising the first 213 of the 252 patients previously reported on[3] This smaller group was followed for a longer period and a different statistical methodology was employed

Patients and methods

Among the patients under 60 years of age who were admitted to the cardiac department at St Vincent s Hospital between January, 1961, and December, 1967 with a first attack of acute coronary insufficiency (ACI) or MI 215 survived for 28 days or longer, two were lost to follow up 213 entered a long term follow up study during which patients were seen annually or more often This report deals with the first 5 years of follow up All patients were given similar treatment in hospital Anticoagulants were not used as part of routine treatment

ACI was diagnosed in patients with typical cardiac pain and serial T wave changes in the electrocardiogram (ECG) without enzyme changes or other indications of heart muscle necrosis[4]

Diagnostic criteria of MI were classical cardiac pain[5] and characteristic ECG and/or typical enzyme changes[4]

Patients with MI were classed as 'complicated' if they presented with supraventricular or ventricular tachyarrhythmias bundle branch block, second degree or complete heart block, prolonged fall in blood pressure cardiogenic shock sustained left ventricular failure, congestive cardiac failure systemic embolism or pericarditis with or without the postinfarction syndrome

Initial factors studied were age at attack, serum cholesterol, in hospital diastolic blood pressure cigarette smoking weight and percentage over weight, and severity of attack (ACI uncomplicated MI or complicated MI) Blood pressure was recorded as the mean of at least three readings taken on the fourth day in hospital Smoking categories used were nonsmoker current smoker, and ex smoker A current smoker was defined as taking five cigarettes or more daily

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any form of medical intervention whether it be by drugs exercise or surgery in any way determines the future life expectation of patients afflicted with CHD

We could find no relation between subsequent nonfatal infarction and the initial factors studied nor was morbidity affected by subsequent cigarette smoking No difference in the mode of death was noted among those decedents who continued, reduced or stopped smoking

Summary

A total of 213 male patients who survived an initial episode of acute coronary insufficiency or myocardial infarction for 28 days have been followed for 5 years The effect of age weight severity of infarction diastolic blood pressure serum cholesterol and cigarette smoking at the time of the initial attack on postinfarction morbidity and death was examined Only severity of infarction adversely influenced the long term mortality rate none of the factors studied was related to subsequent morbidity

The effect of subsequent cigarette smoking on morbidity and death was noted over the 5 year period Smoking did not affect subsequent morbidity but there was an increased death rate among those who continued to smoke This effect of smoking was independent of the severity of infarction Improved long term survival may be predicted for patients who stop or markedly reduce cigarette smoking

REFERENCES

1 Kannel W B Castelli W P and McNamara P M The coronary profile 12 year follow up in the Framingham study J Occup Med. 9 611 1967

2. Cady L D Epidemiology of coronary heart disease Am J Cardiol 20 692 1967

3. Mulcahy R. Hickey N., Graham L, and McKenzie G Factors influencing long term prognosis in male patients surviving a first coronary attack Br Heart J 37 158 1975

4 Mulcahy R. and Hickey N Cigarette smoking habits of patients with coronary heart disease Br Heart J 28 404 1966

5 Burgess A M., Fejfar Z. and Kagan A R Arterial hypertension in ischaemic heart disease Comparison in epidemiological studies WHO Chronicle 16 437 1962.

6 Siegal, S Nonparametric Statistics New York 1956 McGraw Hill Book Company Inc pp 96-104

7 Steel, R and Torrie J Principles and Procedures of Statistics New York 1960 McGraw Hill Book Company Inc p 384

8 Morris J N Heady J A and Barley R G Coronary heart disease in medical practitioners Br Med J 1 503 1952

9 Pell S and D Alonzo C A Immediate mortality and 5-year survival of employed men with first myocardial infarction N Engl J Med 270 915 1964

10 Frank C W., Weinblatt E Shapiro S and Sager R V Prognosis of men with coronary heart disease as related to high blood pressure Circulation 38 432, 1968

11 Zukel W J Cohen B M., Mattingly T W., and Hrubec Z. Survival following first diagnosis of coronary disease AM HEART J 78 159 1969

12 Geismar P., Iversen E Mosbech, J and Deyev K Longterm survival after myocardial infarction A national follow up study of 640 patients in Denmark Int J Epidemiol 2 257 1973

13 Sievers J Myocardial infarction. Clinical features and outcome in 3036 cases, Acta Med Scand 175 Suppl. 406 1963

14 Gordon T Kannel W B McGee D., and Dawber T R Death and coronary attacks in men after giving up cigarette smoking Lancet 2 1345 1974

15 Wilhelmsson C Vedin J A Elmfeldt D., Tibblin G., and Wilhelmsen L. Smoking and myocardial infarction Lancet 1 415 1975

16 Burggraf G W and Parker J O Prognosis in coronary artery disease Angiographic hemodynamic and clinical factors Circulation 51 146 1975

17 Leading Article After a coronary Br Med J 2 103 1975

Initial weight was *significantly* associated with total and CHD deaths ($0.025 < p < 0.050$) (Table I) This association was the opposite to that expected in that normal weight patients fared worse than overweight patients This finding may be spurious since the normal weight patients suffering coronary deaths included a disproportionately large number who continued to smoke

Severity of the initial episode of acute CHD was significantly related to total and CHD deaths ($0.025 < p < 0.05$) (Table II)

Effect of smoking during follow up A total of 188 patients were cigarette smokers at initial attack (Table III) Two ex smokers resumed and were included in the 'continued' category All nonsmokers remained off cigarettes

The CHD mortality rate was significantly greater ($p < 0.05$) in those continuing to smoke *compared to those who reduced or stopped* There was no difference in the incidence of fresh nonfatal coronary attack nor in the mode of coronary death among the different follow up smoking groups

Death in the different smoking groups was examined in relation to severity of the attack The effect of subsequent smoking on death was found to be independent of the severity of the attack evaluated by Bartlett s test (Table IV) The death rate of initial smokers with ACI or *uncomplicated MI who stopped or reduced* smoking was roughly one fifth that of initial smokers with complicated MI who continued to smoke

Discussion

Several other studies have recorded long term survival after acute coronary disease[8,1] Comparison between these studies should be made with caution since they differed in diagnostic criteria sex and age distribution of patients and follow up *methodology*

The present study reports an 82 per cent 5 year survival rate in men under 60 years with the first episode of ACI *or MI The studies which most* closely resemble the present one are those of the H I P group[10] and Zukel and associates[11] These workers report similar survival rates *Our morbid*ity rate was 24 per cent a figure similar to that reported by the H I P group[10]

Of the initial factors studied, only severity of initial attack significantly influenced long term prognosis Other workers[1,13] have found that patients with more severe infarctions are more likely to die within 2 years of the attack Normal weight patients apparently fared worse than those overweight but this finding must be interpreted with *caution because of the heavier follow* up smoking of the lighter patient

Elimination of initial risk factors is the aim of secondary prevention *but little* information is available to substantiate the theoretical benefits of such intervention Of the 188 initial smokers those who stopped smoking or substantially reduced their consumption had less than half the mortality rate of those who failed to do so This effect was independent of the effect of the severity of the initial attack and has previously been *confirmed by us using a different* statistical approach[1] In the Framingham study[14] healthy men who stopped smoking after initial examination *had fewer CHD* episodes *and a lower* mortality rate compared to those who continued to smoke but this favorable experience has only recently been reported by ourselves and the Gothenberg group for patients who had already had an episode of acute CHD[1,15]

It might be contended that the association between cessation of cigarette smoking and improved prognosis is due to some third factor other than severity of initial attack such as age, weight, cholesterol level or blood pressure *However the results of* chi square tests of randomness showed that those stopping were equivalent to a random subsample of the initial smokers

Conclusion

Our findings indicate that the nature of the initial coronary attack and the subsequent smoking experience of the patient bear directly on expectation of life In other studies the only other factor which has been shown to influence prognosis is the nature and extent of the disease in the coronary arteries as determined by arteriography[6] It is now established that three vessel disease and significant obstructive disease in the left coronary artery are associated with an adverse prognosis

Other determinants of prognosis have been reported such as ECG changes or heart size[1] but these may be indices of the severity of the infarc*tion No incontrovertible* evidence exists to suggest that any other patient characteristic or

Table I Serial echograms in 16 patients*

Pt	*Age*	*Sex*	*Etiologic diagnosis*	*Indication for surgery*	*Observation period (wk)*	*Status of last echo*
J A.	20	M	Lymphoma	Eff with tamp	20	Single +
B C	20	M	Viral	Recurrent chest pain	3	Single +
E F	57	F	Idiopathic	None	72	Separate
O F	63	F	PPS	None	28	Single
E. H	41	F	ARF with CRF	Eff with tamp	20	Single +
I I	20	M	Stab wound	Eff with tamp	1	Single +
F J	57	M	ARF with CRF	Eff with tamp	3	Separate‡
R K	51	F	ARF with CRF	None	52	Separate
R. L.	33	M	SBE with ARF	None	2	Separate†
W M	20	M	CRF on dialysis	Eff with tamp	3	Single +
S C	20	F	Idiopathic	None	2	Single
Y V	53	F	ARF with CRF	None	2	Separate
E V J	68	M	TB	Const peri	4	Separate†
D W	23	F	Idiopathic	None	2	Single
F W	31	F	CRF stable	None	8	Separate‡
H D	34	F	PPS	None	96	Separate

ARF = acute renal failure CRF = chronic renal failure PPS = post pericardiotomy syndrome SBE = sub-bacterial endocarditis TB = tuberculosis eff with tamp = recurrent effusion with tamponade const peri = constrictive pericarditis single = fused epicardial pericardial echoes separate = separate epicardial pericardial echoes + = postoperative echogram

†Died.

‡Lost to follow up

ducer was usually positioned in the third or fourth left intercostal space at the left sternal border and perpendicular to the chest wall Serial pictures were taken The intervals between recordings varied from 24 hours to 6 months depending on the clinical status of the patient

In comparing the intensity of sound reflected from the pericardial space three technical variables were considered the sector of the ventricle evaluated beam angle and gain setting We used the mitral valve and endocardial echo to help standardize these three variables In addition we varied the beam angle with each evaluation to see its effect on our interpretation

Fig 1 is a representative echogram in which a single epicardial pericardial echo is visible This finding was noted in each of the postoperative echograms following removal of the pericardial fluid In Patients S C O F and D W the single echo pattern evolved as this clinical evidence of pericarditis abated. In Patients E F R K and H D separate epicardial and pericardial echoes suggested persistent effusion despite the resolution of symptoms of pericardial involvement

Seven patients required surgical intervention Five of the seven had persistent echographic evidence of effusion confirmed at surgery The other two patients to be discussed showed echographic evolution of their disease processes

Results of animal studies When the saline solution was introduced directly into the pericardial space an easily identifiable echo free space was detected (Fig 2) Following removal of saline and introduction of unclotted blood the echo-free space was again easily identifiable and no change in reflected sound was noted When the blood changed from the unclotted to clotted state the appearance of progressively more intense echoes in the pericardial space was noted (Fig 2) Also as the intensity of reflected sound from the pericardial space increased identification of the pericardial echo became more difficult With certain beam angles the pericardial echo could be identified but with some angles the echoes from the pericardium and clotted blood tended to merge making separate identification difficult This difficulty was not encountered with saline or unclotted blood In each of the animals the pericardium showed no significant motion with either unclotted or clotted blood or saline in the pericardial space

Case studies

Case 1 B C a 20-year old student was admitted to the hospital with symptoms of recurrent fever and chest pain of 1 year s duration ST segment changes on his ECG were consistent with pericardial disease Acute and convalescent titers suggested a Coxsackie B viral infection No signs of tamponade or constriction were observed Pericardial strip

The role of serial echocardiography in the evaluation and differential diagnosis of pericardial disease

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Echocardiography is an accepted noninvasive technique for detecting pericardial effusion[1-6] Echocardiographic changes in patients with fibroadhesive pericardial disease have also been described[6] The utilization and interpretation of serial echograms to detect changes in the character of pericardial involvement have yet to be defined Recently, echograms taken on a patient with hemopericardium required different gain settings to define the pericardial space on sequential studies This observation prompted us to institute two studies First we studied dogs with saline clotted blood, and unclotted blood in their pericardial space, second, we began to record serial echograms in patients with pericardial effusions in an effort to determine the usefulness of this technique in detecting changes in the character of the pericardial involvement The purpose of this report is to present the data from the canine study and to discuss serial echographic findings in the patients followed for pericardial effusion

Methods

Animal studies Under general anesthesia three open chested dogs were used to assess changes that occurred on the echogram with saline unclotted blood, and clotted blood in the pericardial space The blood was clotted with thrombin, calcium, and aminocaproic acid Echograms were performed by placing the transducer directly on the anterior parietal pericardium A rapid sequence of echograms was taken as the clot formed Thereafter the pericardium was opened to insure the presence of a uniform clot

Patient studies Sixteen patients suspected of having pericardial disease because of characteristic chest pain enlarging cardiac silhouette and/or ST segment changes in their electrocardiograms (ECG s) were admitted to the study when their echocardiograms demonstrated evidence of pericardial effusion Two or more echograms were performed on each patient Table I outlines the clinical data on the 16 patients

The echographic diagnoses were based upon the demonstration of a relatively echo free space between the pericardial and epicardial echoes In addition to the presence of the echo free space we required that the point at the atrioventricular junction where the presence of the effusion was first detected be visualized All echograms were recorded with a Unirad 100 series instrument A 2 25 MHz 13 mm transducer with pulsed echoes at 1 500 pulses per second was used Permanent records were recorded on Polaroid film or the Cambridge fiberoptic recorder The bed was slightly elevated and the patients were placed in a 30 degree left anterior oblique position For best definition of the pericardial effusion the trans

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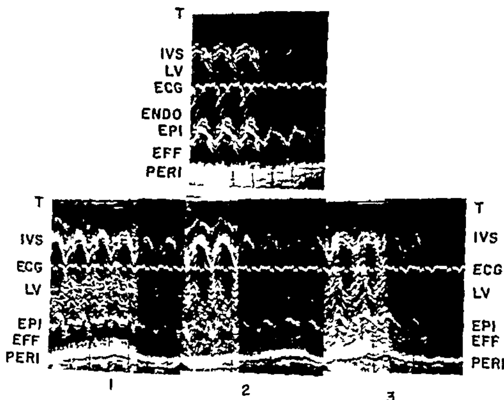


Fig 2 A series of four canine echograms The top is a baseline that demonstrates the amount of reflected sound with unclotted blood or sal ne in the pericardial space Th pictures labeled *1 2 and 3* are a sequential series taken as unclotted blood *in the* peri ardial space coagulated Note the progressive increase in intensity *of reflected* sound in the pericardial space The gain setting *was changed* as the recording *was made* The top picture was taken at a different transducer position The origin of the numerous echoes in the left ventricular cavity was not apparent *EFF* = effusion *EPI* = epicardium and *T* = *transducer*

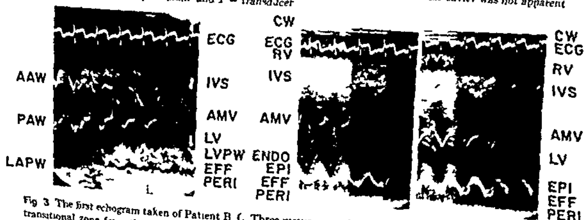


Fig 3 The first echogram taken of Patient B C Three *pictures* are shown The left hand view demonstrates the transitional zone from the left atrial wall to the posterior wall of the *left* ventricle and the *point* where the presence of effusion was first detected The next two views *are at the level* of the mitral valve The *gain setting* was lowered as the picture was taken No pericardial motion is *apparent* *In the* second picture the endocardial echo is barely visible *AAW* = anterior aortic wall, *AMV* = anterior mitral valve *CW* = chest wall *LAPW* = left atrial posterior wall, *LVPW* = left *ventricular* posterior wall *PAW* = posterior aortic wall *RV* = right ventricle

the pericardial sac (3) narrowing of the echo free pericardial space represents fluid re orption from the space We will discuss these changes in further detail in the following paragraphs

Changes in reflected sound Other investigators have evaluated differences in reflected sound intensities of clotted and unclotted blood Edler[4] produced an increase in reflected sound from the left ventricular cavity when a clot was introduced into that chamber He felt the increased intensity of reflected sound occurred because a heterogenous clot produces multiple acoustical interfaces

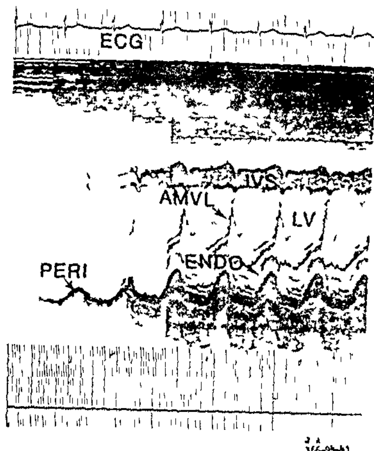


Fig 1 An echogram of Patient J A taken after surgical removal of pericardial fluid A single pericardial epicardial echo is consistent with the absence of effusion The gain setting was changed as the recording was made *AMVL* = anterior mitral valve leaflet *FCG* = electrocardiogram *ENDO* = endocardium *IVS* = interventricular septum *LV* = left ventricle and *PERI* = pericardium

ping was eventually advised because of recurrent disabling symptoms

Echographic findings Three echograms were recorded at weekly intervals The last echogram was taken just prior to surgery and was recorded with a fiberoptic recorder The first echogram demonstrated an echo free space without pericardial motion a pattern consistent with pericardial effusion (Fig 3) The second echogram demonstrated systolic anterior pericardial motion without a change in the distance between the epicardial and pericardial echoes (Fig 4) The third echogram again showed systolic anterior pericardial motion a well as narrowing of the distance between the epicardial and pericardial echoes (from 10 to 3 mm) and a change in sound intensity reflected from the pericardial space (Fig 5) During each echogram one tracing was taken with the gain purposely set to record only faint and incomplete endocardial echoes Using this setting as a standard the first two echograms showed the pericardial space to contain only faint echoes or to be echo free However in the third study dense echoes became visible in the pericardial space The area of the pericardium evaluated in each tracing was posterior to the mitral valve leaflets Following the third echogram pericardiectomy confirmed the diagnosis of a fibroadhesive pericarditis The thickness of the pericardium was reported to be 5 to 6 mm

Case 2 E V J a 68 year old man was admitted to the hospital because of chest pain dyspnea and malaise of 2 weeks duration Evaluation on admission revealed an elevated temperature (100 to 103 F) atrial fibrillation nonspecific ST segment changes and an enlarged cardiac silhouette One week after hospital admission a pericardial friction rub was detected During his hospital stay he developed an elevated venous pressure with associated edema ascites and pleural effusion A venous pulse tracing revealed an early V peak with a dip plateau wave form in early diastole No third sound was heard

E V J s clinical course was consistent with that of a patient who initially had a constricting process The rapid progression of this fibrotic progress has been previously documented by other investigators

Echographic findings The first series of three echograms demonstrated a pattern consistent with pericardial effusion an echo free space was discernible the point at the atrial ventricular junction where the presence of effusion was first detected was apparent and there was no pericardial motion (Fig 6) Inspection of the epicardial echo revealed two parallel moving lines 1 mm apart Following the echogram the presence of pericardial fluid was documented by pericardial tap

The second echogram taken 2 weeks later demonstrated the importance of beam angle in identifying anatomical structures (Fig 7) The epicardial echo appeared as a single echo with one beam angle and double with another With the first beam angle the pericardial echo could be identified easily with the second the pericardial echo was difficult to identify

The third echographic series taken just prior to surgery revealed the following changes (Fig 8) The pericardial echo developed systolic anterior motion and multiple parallel moving echoes appeared between the epicardial and pericardial echoes At a gain setting and beam angle that barely visualized the endocardial echo the pericardial space was filled with echoes instead of remaining echo free These changes were evaluated in the area of the pericardium posterior to the tips of the mitral valve leaflets

At surgery a fibrotic constrictive pericarditis without fluid was noted and pericardiectomy was performed The fibrous coat was estimated to be about 8 mm thick anteriorly and 15 mm thick posteriorly The pathology report revealed tuberculous pericarditis

Discussion

Serial changes In performing serial echograms in patients with pericardial effusion the following changes were detected (1) variations in the intensity of reflected sound from the pericardial space despite a standardized gain setting (2) appearance of systolic anterior motion of a previously unmoving pericardial echo (3) decrease in dimension of the echo free pericardial space From our correlation of these changes with surgical findings and animal studies we have evidence to support the following assumptions (1) a change in the intensity of reflected sound from the pericardial space represents a change in the homogeneity of the contents of the space (2) the occurrence of systolic anterior pericardial motion suggests the development of adhesions between the epicardial and pericardial layers of

Our canine studies confirm his findings We applied this principle to other substances with the assumption that the replacement of a serous effusion by fibrous material (a less homogenous substance) would increase the intensity of sound reflected from the pericardial space

In addition to changes in the homogeneity of the contents of the pericardial space alterations of the beam angle or gain setting may vary the intensity of reflected sound We utilized the method noted previously to standardize these factors

Pericardial wall motion Systolic anterior motion of the pericardial echo has been reported in patients with fibroadhesive pericardial disease Horowitz and associates felt that the motion of the pericardial echo may be related to the development of adhesions between the visceral and parietal layers of the pericardium

Two of our patients B C and E V J who initially had nonmoving pericardial echoes later developed systolic anterior pericardial motion as shown on their presurgical echograms At the time the nonmoving echo was noted in Patient E V J we documented the presence of pericardial fluid by pericardiocentesis in Patient B C we relied solely on the echographic pattern for diagnosis Later as systolic anterior pericardial motion occurred in both patients we documented the replacement of fluid with fibrotic tissue by surgical observation Associated with the presence of systolic anterior pericardial motion in both Patients B C and E V J was an increase in intensity of sound reflected from the pericardial space despite a standardized gain setting To date these two findings seem helpful in evaluating the replacement of fluid by a fibrotic state

Findings of pericardial fibrosis Reports on the presence of abnormal pericardial echoes in the presence of fibrotic constrictive pericardial disease have varied Gibson and associates reported that they were unable to detect an abnormal pericardial thickening in their group of patients with constrictive disease Horowitz and associates noted two parallel moving echoes 1 to 3 mm apart in the vicinity of the constrictive pericardial layer In those patients with epicardial constriction and effusion the abnormal echoes were noted in the vicinity of the epicardial echo In the patients without effusion the abnormal echo pattern was noted in the vicinity of the pericardial echo Our experience would indicate

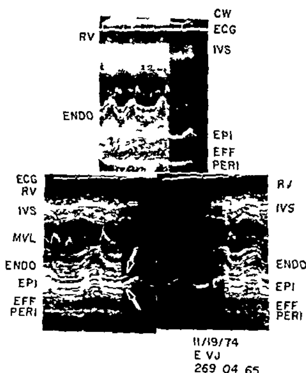


Fig 7 The second echogram taken on Patient E V J The top picture demonstrates the pericardial echo as an identifiable structure 7 cm posterior to the epicardium The two pictures below are taken just after the top picture but at different transducer angles The two lower pictures were recorded at 50 mm per second the upper at 25 mm per second The pericardial echo is difficult to identify in the bottom two pictures but the arrows identify two parallel moving echoes 1 mm apart *EFF* = effusion or fibrosis

that an important factor in the determination of pericardial abnormalities is recording technique Two important recording techniques are proper adjustment of beam angle and gain setting In Patient E V J s second series of echograms the proper identification of the pericardial echo was dependent upon beam angle (Fig 7) In Patient B C s presurgical echogram the identification of two strong parallel moving echoes 3 mm apart in the vicinity of the pericardial echo may have been enhanced by adjusting the gain setting to obtain more echo attenuation (Fig 5) In both patients in addition to the usual echocardiographic methods of identifying pericardial effusion serial tracings were standardized by carefully adjusting the beam angle and gain setting to record only faint and incomplete endocardial echoes

In addition to recording techniques we would anticipate that differences in the characteristics of the fibrotic process may alter echographic appearances The homogeneity as well as the

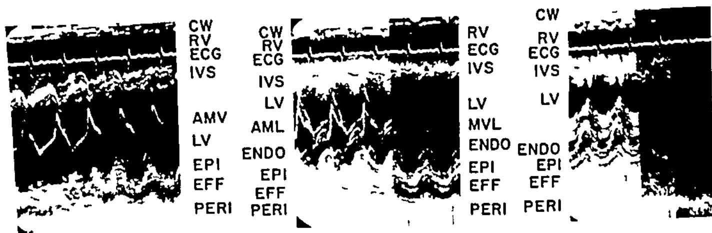


Fig 4 The second echogram taken of Patient B C From left to right the first view shows the left atrial posterior left ventricular wall transition zone The second and third show areas at the level of the mitral leaflets and chordae Anterior systolic motion of the pericardial echo is apparent The gain setting was changed as the pictures were taken The endocardial echo is barely visible after the first gain change *MVL* = mitral valve leaflet

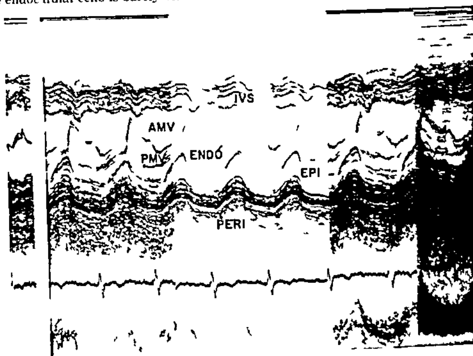


Fig 5 The third echogram was taken on Patient B C with a different recorder This echogram was taken in the area of the mitral valve leaflet Different gain settings are recorded At the second gain setting the endocardial echo is barely visible but intense sound is reflected from the pericardial space *PMV* = posterior mitral valve

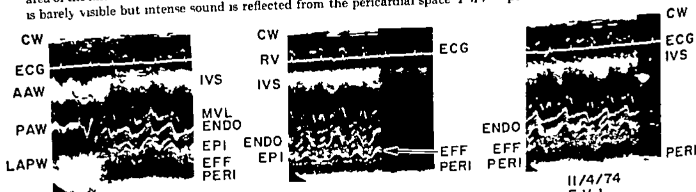


Fig 6 First echogram on Patient E V J From left to right the first view demonstrates the transition zone between the left atrial wall and the posterior left ventricular wall The point where the presence of effusion was first detected is apparent The second and third pictures are taken at the level of the chordae As the picture is recorded different gain settings are used The arrow identifies two parallel moving echoes 1 mm apart

5 Goldberg B B Ostrum B J and Isard H J Ultrasonic determination of pericardial effusion J A M A 202 9? 1967
6 Horowitz M S Schultz C S Stinson E B Harrison D C and Popp R L Sensitivity and specificity of echocardiographic diagnosis of pericardial effusion Circulation 50 39 1974
Hancock E W Subacute effusive constrictive pericarditis Circulation 43 183 1971
8 Edler I Echograms from the isolated heart thrombi and vessel walls Acta Med Scand 170 Suppl. 370 (chap VI) 51 1961
9 Gibson T C Grossman W., McLaurin L. P., and Craige E Echocardiography in patients with constrictive pericarditis (abst) Circulation 49 50(Suppl. 3) 86 1974
10 Horowitz M S., Rossen R M Harrison D C., and Popp R L. Ultrasonic evaluation of constrictive pericardial disease (abst) Circulation 49 50 (Suppl 3) 87 1974

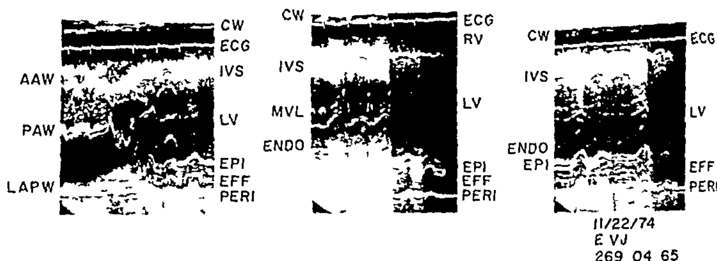


Fig 8 The third echogram of Patient E V J was taken just prior to surgery From left to right the first view shows the transition from the left atrial wall to the posterior wall of the left ventricle The second picture was taken at the level of the mitral valve leaflets the third at the chordae level The increased echo intensity and multiple parallel moving echoes of the area labeled effusion now represent fibrosis Systolic anterior motion of the pericardial echo is noted

degree of adhesiveness of the fibrotic layers may vary not only from patient to patient but serially in the same patient

Our findings demonstrate that serial echographic changes take place in some patients with pericardial disease Based on our experience we would urge the use of serial echograms in the follow up evaluation of all patients with pericardial effusion Serial echograms may also be useful in defining the coagulation state of hemopericardium Serial studies should be continued until resolution of the disease takes place or surgical intervention is required The interval between studies should be determined by the clinical state of the patient Further studies correlating serial echographic changes with surgical and pathological findings will undoubtedly improve the definition and reliability of our interpretations

Summary

Echocardiography is an established method for the diagnosis of pericardial effusion Echographic findings in fibroadhesive disease have also been described The interpretation of a changing serial echogram during the clinical course of pericardial disease has not been established

Sixteen patients with echographic evidence of pericardial effusion were followed with serial echographic studies In seven surgical or autopsy correlation was obtained Because of the serial changes noted we undertook a study in dogs to clarify the problem of variability in intensity of sound reflected from the pericardial space

Three open chested dogs were studied with rapid sequence surface echograms as blood introduced into the pericardial space was converted from the unclotted to the clotted state In all three dogs blood clotting increased the intensity of sound reflected from the pericardial space

Our study of two patients with fibroadhesive pericardial disease documents serial changes in echoes from the pericardium and pericardial space accompanying the clinical evolution of the disease process and suggests a method for avoiding the commonly encountered difficulty in proper identification of the pericardial and epicardial echoes

Our preliminary studies suggest that serial echograms should play an important role in the management of patients with pericardial effusion further surgical/pathological correlations are required

The authors wish to express heartfelt thanks to Irma Larsen Robert Dickerson and Charlene Broock for their assistance and to Dr Stanley Wishner for providing the echocardiogram for Fig 5

REFERENCES

1 Edler I The diagnostic use of ultrasound in heart disease Acta Med Scand Suppl 308 32 1955
2 Feigenbaum H Waldhausen J A and Hyde L P Ultrasonic diagnosis of pericardial effusion J A M A 191 711 1965
3 Feigenbaum H Zaky A and Waldhausen J A Use of reflected ultrasound in detecting pericardial effusion Am J Cardiol 19 84 1967
4 Moss A J and Bruhn F The echocardiogram An ultrasound technic for the detection of pericardial effusion N Engl J Med 274 380 1966

patients) and/or findings at embolectomy (23 patients) There were six men and 27 women their average age was 43 years (21 to 68 years)

2 **Medical treatment** Over the same period of time there were 35 patients with angiographically proved isolated acute massive pulmonary embolism (as defined above) in whom the primary treatment was with heparin (18 patients) or streptokinase (17 patients) Details of administration and dosage of heparin or streptokinase have been described elsewhere[3] but are summarized briefly below Following pulmonary arteriography a catheter was left in position in the main pulmonary artery for 72 hours and used for infusion of either (1) streptokinase (Kabikinase) 600 000 units in the first 30 minutes followed by 100 000 units per hour (2) heparin 5 000 units in the first 30 minutes followed by 2 500 units per hour for 72 hours Following the demonstration by Barritt and Jordan of the protective effect of heparin in acute pulmonary embolism it is probably unethical to withhold heparin unless alternative therapy (e g streptokinase) is employed It is for this reason that heparin was administered to the control group In some but not all of these patients treatment was selected on a random basis The results of medical treatment are summarized here for purposes of comparison with the results of embolectomy In the heparin treated group there were seven men and 11 women their average age was 52 years (38 to 69 years) In the streptokinase treated group there were five men and 12 women their average age was 49 years (19 to 71 years)

3 **Shock / Nonshock** All 68 patients were divided into two groups according to the presence or absence of shock defined as a systolic arterial pressure of 100 mm Hg or less (In one "shock patient undergoing embolectomy pressure was above this level but could only be maintained by a continuous infusion of large doses of metaraminol) These categories were determined in relation to the patients state *at the time when primary treatment was initiated by us—i.e* referral for embolectomy or the institution of heparin or streptokinase therapy Many patients had a low or unrecordable blood pressure with the onset of embolism but were in a stable state with a blood pressure of over 100 mm Hg systolic by the time they were transferred to our hospital Such patients are not categorized as having shock Conversely some patients became hypotensive after arrival and are categorized as having shock if this was their state when specific therapy was instituted at this hospital

4 **Treatment failures** It is our practice that when a patient deteriorates during medical treatment alternative measures are employed (Streptokinase or embolectomy when the primary treatment is with heparin embolectomy when it is with streptokinase) Thus the mortality rate for medical treatment may appear falsely low due to the potential which alternative treatment may have for retrieving a deteriorating situation For this reason we report both the actual mortality figures and the treatment failures Treatment failure refers to the situation of hemodynamic deterioration (falling arterial pressure or continued intolerably low levels of arterial pressure) which lead to substitution of alternative therapy Episodes of recurrent embolism are included as treatment failures

Results

For the whole group the over all mortality rate was 16 per cent (11 of 68)

Nonshock 27 patients (Table I)

1 *Primary treatment—pulmonary embolectomy* 10 patients One patient in this group died (mortality rate 10 per cent)

CAUSE OF DEATH Circulatory arrest occurred during induction of anesthesia The patient died 7 days later without having regained consciousness This patient is discussed more fully below

2 *Primary treatment—streptokinase* nine patients No deaths and no treatment failures occurred in this group

3 *Primary treatment—heparin* eight patients One patient had a gastrointestinal hemorrhage during heparin therapy which was therefore abandoned and embolectomy was performed Oral anticoagulants were given in the postoperative period and he died 9 days after the original embolus from a further gastrointestinal hemorrhage despite a satisfactory prothrombin ratio

One patient became hypotensive after 7 days of heparin due to bleeding from a hysterectomy wound and gastrointestinal hemorrhage Embolectomy was successfully carried out after blood transfusion

One patient suffered a nonfatal recurrent embolism for which he was then treated with streptokinase

Pulmonary embolectomy, heparın, and streptokınase Theır place ın the treatment of acute massıve pulmonary embolısm

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The place of pulmonary embolectomy ın the treatment of pulmonary embolısm has been the subject of much dıscussıon but few definıte conclusıons sınce a randomızed trıal of embolec tomy and alternatıve treatment does not seem feasıble [1] Our reasons for addıng to the already volumınous lıterature on the subject are as follows

1 In most serıes the mortalıty rate quoted for pulmonary embolectomy ıs, ın our vıew consıder ably hıgher than can be achıeved thus provıdıng a false basıs for comparıson wıth other forms of treatment

2 It has been suggested that pulmonary embo lectomy ıs seldom both technıcally feasıble and clınıcally approprıate In one serıes of 45 patıents wıth massıve pulmonary embolısm[2] there were only four ın whom embolectomy was judged to be technıcally feasıble All four had another lethal condıtıon such as metastatıc neoplasm or end stage cırrhosıs whıch made embolectomy ınappro prıate The present serıes ıncludes 23 patıents ın shock ın whom embolectomy *was* performed none had termınal carcınomatosıs or sımılar contraındıcatıon to embolectomy

3 Our own relatıvely large serıes of patıents (68 wıth ısolated actıve massıve pulmonary embolısm reported here) have been treated by embolectomy or medıcally wıth antıcoagulants or streptokı nase, thus permıttıng some comparıson between the dıfferent treatment regımes As a result of thıs experıence we have developed an approach to treatment selectıon whıch ıncludes a place for pulmonary embolectomy

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Case materıal and definıtıons

1 Pulmonary embolectomy Sınce June, 1964 a total of 53 patıents wıth massıve pulmonary embolısm have undergone emergency embolec tomy wıth total cardıopulmonary bypass Of these, 20 had assocıated cardıorespıratory dısease or had embolısm of uncertaın duratıon and have been excluded from thıs study The remaınıng 33 patıents, ın whom the prımary* treatment was pulmonary embolectomy, had *ısolated acute massıve pulmonary embolısm*, as defined below These 33 patıents together wıth 35 medıcally treated patıents wıth ısolated acute massıve pulmonary embolısm form the basıs of thıs report

Isolated No patıent had any other cardıorespı ratory dısease

Acute All patıents were admıtted and specıfic treatment was begun 2 to 48 hours from the onset of symptoms of massıve embolısm

Massıve pulmonary embolısm Involved at least 50 per cent of the pulmonary arterıal tree as demonstrated by pulmonary arterıography (10

Prımary treatment refers to the specıfic treatment ınıtıally employed by us final treatment may be dıfferent Thus of the 18 patıents ın whom heparın was the prımary treatment adopted fi e had a subse quent embolectomy
Prımary treatment ıgnores treatment gıven at the referrıng hospıtal although five of the patıents treated by embolectomy had been gı en heparın at the referrıng hospıtal for perıods rangıng from 2 to 48 hours

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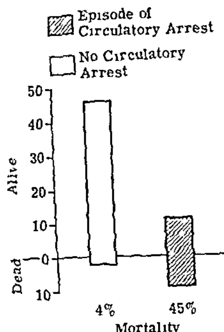


Fig 1 The adverse effect of an episode of circulatory arrest on mortality rate in 68 patients with isolated acute massive pulmonary embolism

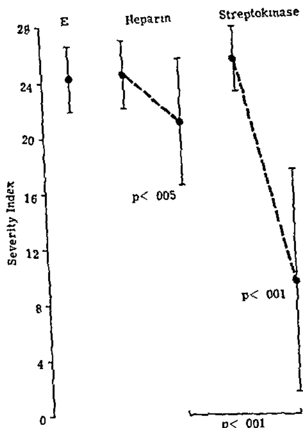


Fig 2 The response to treatment as assessed by angiographic appearances before and after 72 hours of treatment Vertical axis shows numerical index of severity obtained from pulmonary arteriograms For method of scoring see Miller and associates and Tibbutt and associates Mean values for each group and 1 S D are shown Broken lines join the pre and posttreatment values for the heparin treated and streptokinase treated groups No posttreatment values are available for the patients who were treated by embolectomy but the preoperative index of severity was similar for these and for the medically treated patients

prior to institution of specific therapy The mortality rate in these patients was 45 per cent (nine of 20) embolectomy seven of 14 streptokinase one of three heparin one of three) Only two (4%) of the 48 patients who had not suffered a circulatory arrest died none of these deaths was in the embolectomy group (One of these two deaths occurred in the heparin and one in the streptokinase group)

In four patients external cardiac massage was unsuccessful in restoring a stable hemodynamic state and had to be continued in the operating theater up to the time of institution of total cardiopulmonary bypass all four patients died

Rate of resolution—medically treated patients (Fig 2) The effect of streptokinase in accelerating resolution has been reported elsewhere In the present series of patients not all treated on a random basis the same effect was observed Fig 2 shows the angiographically determined degree of resolution after 72 hours of treatment in the heparin and streptokinase treated patients who completed their primary treatment Resolution was significantly ($p < 0.001$) more complete at 72 hours in the streptokinase than in the heparin treated group This figure also shows that the initial angiographic assessment of severity of embolism was similar for all three treatment groups

Late deaths Five of the 57 survivors had subsequently died 9 to 87 months after the initial embolic episode four died from neoplastic disease (known to be present at the time of pulmonary embolism in only two) and one from a probable myocardial infarct though recurrent massive pulmonary embolism cannot be excluded as the cause of death in this patient who died suddenly 30 months after streptokinase treatment of the original massive embolus Details of the late follow up of these patients will be reported elsewhere

Discussion

It is well known that some two thirds of patients who die from pulmonary embolism do so within the first 2 hours[4] and that coexisting

Table I 'Nonshock '–B P > 100 mm Hg

Primary treatment	*Embolectomy*	*Streptokinase*	*Heparin*	*Total*
Total number of patients	10	9	8	27
Deaths	1	0	1	2 (7 4%)
Treatment failure	–	0	1	
Recurrent embolism	0	0	1	1
Total deaths and failures	1 (10%)	0	3 (37 5%)	

Table II "Shock –B P < 100 mm Hg

Primary treatment	*Embolectomy*	*Streptokinase*	*Heparin*	*Total*
Total number of patients	23	8	10	41
Deaths	6	1 (2)	1	9 (21 9%)
Treatment failure	–	1	4	
Recurrent embolism	0	1	1†	2
Total deaths and failures	6 (26%)	2 (25%)	5 (50%)	

This patient failed treatment (haemodynamic deterioration) but died 3 months later of a recurrent embolus He therefore appears in the failure and recurrent columns and (in brackets) in deaths

†This patient died of recurrent embolism and also appears in the deaths column

The combined death/treatment failure rate was therefore 37 5 per cent

Shock 41 patients (Table II)

1 *Primary treatment–pulmonary embolectomy* 23 patients Six patients in this group died (mortality rate 26 per cent)

CAUSES OF DEATH All patients who died had suffered at least one episode of circulatory arrest prior to surgery (Of the 17 survivors in this group five had suffered an episode of circulatory arrest)

Three deaths were neurologic, i e, the patients came off bypass in a satisfactory state but died 2 to 28 days later without having regained consciousness Two of these patients were unconscious on arrival from the referring hospital (one was hemiplegic) In the other blood pressure was unrecordable at the time of referral for embolectomy and cardiopulmonary bypass was established while cardiac massage was being performed

Two further patients died in the operating theater both, with unrecordable blood pressure were having external massage while cardiopulmonary bypass for embolectomy was being established The last patient who died had severe intra abdominal hemorrhage as a result of a lacerated liver caused by preoperative resuscitative efforts and had fixed dilated pupils prior to operation

2 *Primary treatment–streptokinase* eight patients One patient in this group died one patient deteriorated (treatment failure) and eventually died of a recurrent embolus 3 months later The combined death/treatment failure rate was therefore 25 per cent

CAUSES OF DEATH One patient was unconscious on admission because of a prior circulatory arrest, and died 3 months later never having regained consciousness, despite complete hemodynamic recovery with streptokinase The other patient remained hypotensive after 12 hours treatment with streptokinase and was therefore submitted to embolectomy (= treatment failure) Convalescence was complicated by bleeding leading to hypotension and renal failure for which hemodialysis was successfully performed at another hospital During convalescence he suffered a further pulmonary embolus and inferior vena caval plication was carried out Two months after his first massive embolus and just prior to discharge he suffered a third– and fatal–pulmonary embolus despite inferior vena caval (IVC) plication

3 *Primary treatment–heparin* 10 patients One patient in this group died There were four treatment failures (hemodynamic deterioration leading to alternative treatment–embolectomy two streptokinase two) The combined death/treatment failure rate was therefore 50 per cent

CAUSES OF DEATH One patient died of a recurrent embolus at 6 days Emergency embolectomy was performed while external massage was being carried out but was unsuccessful

The effect of previous circulatory arrest (Fig 1) In the whole group of 68 patients 20 had suffered at least one episode of circulatory arrest

the reduced indications for embolectomy and the consequent sharp reduction in the number of embolectomies currently performed by us is a result of an appreciation of the value of strepto kinase Were this treatment not available embo lectomy would still in our view be indicated for a significant number of patients—those with mas sive embolism in shock

Finally we may speculate about the deaths Need they have occurred? As a simplification we may say that of the 11 patients who died in the whole group of 68 patients (over all mortality rate 16 per cent) three were unconscious on arrival because of cerebral anoxia sustained during a prior circulatory arrest and were probably unrecoverable One died of a complica tion of anticoagulant therapy The remaining seven patients died either of a recurrent embolus (two patients) or because circulatory arrest occurred shortly before transfer to the operating room or on induction of anesthesia Might these seven lives have been saved? Reul and Beall[12] and Beall and Collins[3] have advocated the use of partial (femorofemoral) bypass as the initial step in patients who have sustained a circulatory arrest and report seven survivors out of nine patients where this technique was used seven of the nine had presented with circulatory arrest Although it is probably no quicker to establish partial bypass than to establish complete bypass with aortic and atrial cannulation the efficacy of cardiac massage must be considerably reduced during the latter procedure It is possible that some of the patients in our series who died because circulatory arrest occurred shortly before surgery might have survived if this technique had been adopted

IVC interruption has been advocated for all patients who survive massive pulmonary embo lism and it has been suggested that the incidence of recurrent embolism is as high as 30 per cent or more when this treatment is not employed Our experience would suggest that in energetically treated patients the incidence of recurrent embolism is extremely low—three of 68 (4 per cent) in this series—and in one of the two patients who had a fatal recurrent embolus this occurred after IVC plication had been performed It seems likely that the low recurrence rate can be attributed to over all energetic treatment includ ing the use of anticoagulants or streptokinase Claims that operations on the IVC have been the cause of a low mortality rate from pulmonary embolism must take such considerations into account[13] We see no place for an operation with significant morbidity mortality and recurrence rates not significantly less than the 4 per cent recurrence rate reported here[14]

In summary we believe that the treatment given to a patient who has suffered an acute massive pulmonary embolus should be tailored to his condition In the patient who cannot be adequately resuscitated after suffering a circula tory arrest or who is deteriorating rapidly despite thrombolytic therapy there is no alternative to pulmonary embolectomy the partial bypass technique advocated by Beall and Collins[13] may help to reduce the mortality rate in this group We do not have experience of the partial bypass technique in this situation In the patient who has survived for 2 hours or more but is in shock it is our present policy to use streptokinase as the treatment of first choice since a survival rate of 75 per cent can be expected with either embolec tomy or thrombolytic therapy Embolectomy is still however needed for patients in this group in whom there is a specific contraindication to thrombolytic therapy and in those patients who deteriorate despite thrombolytic therapy Finally in the patient with acute massive embolism who is not in shock we employ streptokinase since we have not observed treatment failure with this therapy whereas we find that conventional heparin therapy is still associated with occasional treatment failures The mortality rate in this group should be extremely low

Finally it must be admitted that the ability to tailor treatment to the patient s state depends as regards embolectomy on the 24 hour availability of a cardiac surgical team experienced in this operation Perhaps the most important fact to emerge from this study is the comparable effec tiveness of streptokinase as a method of treat- ment which is available in all hospitals in the United Kingdom With such treatment one would expect that only an occasional patient will still require emergency embolectomy

The results reported here reflect the skills of many members of the cardiac and cardiac surgical teams at the Brompton Hospital in particular we wish to acknowledge the contribu tion of Drs R Gibson M Honey and D Gibson under whose care the patients were admitted and managed and Mr S Lennox who performed some of the embolectomies To these and others with whom we have shared our experience we wish to acknowledge our debt

cardiorespiratory disease adversely affects prognosis.[7] We freely admit that our patients, having all survived 2 hours or more* and not having other cardiorespiratory disease, are a selected group with a relatively favorable prognosis. The issue is, "Did pulmonary embolectomy save the lives of any patients who would have died without this treatment? (or even more critically, Did pulmonary embolectomy actually contribute to the death of a patient who would otherwise have survived?)" Linked with this question is another: "Is there an alternative form of treatment which is equally effective?"

Clearly the present study cannot answer such questions in a way that would satisfy a statistician; the numbers dying in each group are small and treatment was not allocated on a random basis. Most importantly, alternative treatment was employed when a patient deteriorated during medical treatment, thus introducing an element of speculation about what *might* have happened if embolectomy had not been available. None the less we believe that some useful facts emerge from this series.

1. In patients with massive pulmonary embolism who have survived 2 hours or more and are not in shock the mortality rate is low: two of the 27 patients in this category died and both deaths were avoidable. One died from a complication (bleeding) of anticoagulant therapy and one died as a result of a circulatory arrest occurring during induction of anesthesia for embolectomy. The latter patient was seen early in our experience when the effects of anesthesia and vasodilation on a patient critically dependent on enhanced vascular tone were not appreciated. This risk is now appreciated and vasopressor drugs are administered prior to induction of anesthesia. At the present time, however, we would not employ embolectomy for patients not in shock. Whether or not there is anything to choose between streptokinase or conventional anticoagulant therapy in this group is debatable. No problems were encountered in the streptokinase treated "nonshock" group whereas one of the heparin treated patients died, one had a nonfatal recurrent embolus, and one deteriorated (progressive hypotension) during therapy and had a successful embolectomy. This small experience is insufficient to permit conclusions about the best treatment in this good risk group; none the less it is our practice to employ streptokinase for such patients; resolution will be accelerated and the risk of deterioration may be minimized. In addition, streptokinase effectively dissolves "dangerous" thrombus in the iliofemoral segment,[8] thereby decreasing the chance of significant recurrent embolism.

2. In patients with massive pulmonary embolism who have survived for 2 hours but are in shock it is our experience that treatment with heparin is associated with a high (50 per cent) failure rate; one patient died from a recurrent embolus and no less than four of the 10 patients deteriorated and were judged to be in danger of death (all four survived after alternative treatment had been instituted). It was our practice before thrombolytic therapy was available to employ embolectomy for this group; subsequently streptokinase has been employed and the combined death/failure rate for streptokinase is the same as the mortality rate for embolectomy (25 per cent and 26 per cent, respectively). We believe that either embolectomy or streptokinase is justified in these patients who fulfill in general the indications of Sasahara and Barsamian[4] for embolectomy, namely, a systolic blood pressure of less than 90 mm Hg, urine output less than 20 ml per hour, and arterial P_{O_2} less than 60 mm Hg after 1 hour of maximum medical management. The mortality rate from embolectomy in this group is not, as has been suggested, of the order of 40 to 60 per cent,[11] but is 26 per cent overall and zero when no episode of circulatory arrest has occurred. A factor which must be of great importance in determining the mortality rate from embolectomy is the time elapsed between embolism and surgery. This is not always stated in reported series but it is of interest that in one series[11] with a comparable elapsed time (7+ hours) the mortality rate (23 per cent) was identical to that reported here. It is probable that streptokinase is equally good treatment *provided* that embolectomy is available (1) for the occasional patient who deteriorates despite streptokinase and (2) for the patient with massive embolism in shock in whom streptokinase is contraindicated, e.g., in a patient who has had surgery within the preceding 48 hours. It is these two types of patient for whom we still employ embolectomy today. It must be emphasized that

*The mean interval between onset of embolism and embolectomy was 11.9 hours in the "shock" group and 25.6 hours in the "nonshock" group.

Echocardiographic criteria for the diagnosis of mitral semilunar valve continuity

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Normally the anterior mitral valve leaflet (AMVL) is in fibrous continuity with the left and noncoronary cusps of the aortic valve[1] This relationship has been extensively studied and established by angiography Halleman and associates reported that the AMVL and the posterior aortic root (PAR) form virtually a straight line on the lateral angiocardiogram during ventricular systole This anatomical continuity can be demonstrated echocardiographically by sweeping the transducer from the apex to the base of the heart

It has been suggested by Chesler Tajik[4] and Gramiak and their colleagues that the AMVL and the PAR echocardiographically are continuous and are also found at the same depth when measured from the chest wall echoes In the past the observation that the AMVL and the PAR lay at approximately the same depth has been considered evidence for mitral semilunar valve continuity The purpose of this study is to determine the normal expected distance between the plane of the mitral valve and the plane of the semilunar valve and to ascertain the echocardiographic criteria necessary to determine whether or not the mitral and semilunar valves are echocardiographically continuous

Methods

Thirty nine healthy individuals who denied any history of cardiac disease and who had no evidence of cardiovascular disease on physical examination were prospectively studied by cardiac ultrasound There were 31 men and eight women ranging in age from 19 to 47 years

The ultrasonic beam was slowly rotated to record a continuous sweep from the AMVL in the left ventricular and left atrial areas to the aorta at the level of the aortic leaflets (Fig 1) [5] [7] All patients were studied in the third and fourth left intercostal spaces in both the supine (SUP) and the 30 degrees left lateral (LL) positions

As is shown in Fig 1 measurements were made from the chest wall transducer echoes (CW) to the following points (1) the closing point (C) of the AMVL in the left ventricular area (line *a*) denoted as CW AMVL (LV) (2) the closing point of the AMVL in the left atrial area (line *b*) denoted as CW AMVL (LA), and (3) the maximal posterior excursions of the posterior aortic root (PAR) at end diastole at the level of the aortic leaflets (line *c*) denoted as CW PAR (DIA)

The differences in the depth of the *c point* of the AMVL in the left ventricular area and the depth of the most posterior excursion of the PAR at the level of the aortic leaflets were calculated at end diastole and are defined as CW AMVL (LV) – CW PAR (DIA) Similarly the differences in the depth of the c point of the AMVL in the left atrial area and the depth of the most posterior excursion of the PAR at the level of the aortic leaflets were calculated at end diastole and are defined as CW AMVL (LA) – CW PAR (DIA)

Materials

A commercially available Unirad C series echocardiograph with a Tektronix model 174 strip recorder was used Two 2 25 megahertz transducers focused at either 7 5 or 10 cm were used in

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REFERENCES

1 Sautter R D Myers W O Ray J F and Wenzel F J Pulmonary embolectomy Review and current status Prog Cardiovasc Dis 17 371 1975
2 Alpert J S Smith R E Ockene I S Askenazi J Dexter L and Dalen J E Treatment of massive pulmonary embolism The role of pulmonary embolectomy Am Heart J 89 413 1975
3 Miller G A H Sutton G C Kerr I H Gibson R V and Honey M Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary emboism Br Med J 2 681 1971
4 Tibbutt D A Davies J A Anderson J A Fletcher E W L Hamill J Holt J M Lea Thomas M Lee G de J Miller G A H Sharp A A and Sutton G C Comparison by controlled clinical trial of streptokinase and heparin in treatment of life threatening pulmonary embolism Br Med J 1 343 1974
5 Hall R Sutton G C and Kerr I H Resolution of pulmonary embolism Circulation 52 (Suppl II) 131 1975
6 Gorham L W A study of pulmonary embolism Arch Intern Med 108 8 1961
7 Murphy M L and Bulloch R T Resolution of pulmonary emboli as determined by angiography and scanning Clin Res 15 348 1967
8 Mavor G F Dhall D P Dawson A A Duthie J S Walker M G Mahaffy R G and Alardyce M Streptokinase therapy in deep vein thrombosis Br J Surg 60 468 1973
9 Sasahara A A and Barsamian E M Another look at pulmonary embolectomy Ann Thorac Surg 16 317 1973
10 Cross F S and Mowlem A A survey of the current status of pulmonary embolectomy for massive pulmonary embolism Circulation 35 (Suppl I) 86 1967
11 Berger R L Pulmonary embolectomy with preoperative circulatory support Ann Thorac Surg 16 217 1973
12 Reul G J and Beall A C Emergency pulmonary embolectomy for massive pulmonary embolism Circulation 50 (Suppl II) 236 1974
13 Beall A C and Collins J J What is the role of pulmonary embolectomy? Am Heart J 89 411 1975
14 Crane C Hartsuck J Birtch A Couch N P Zollinger R Matloff R Dalen J and Dexter L The management of major pulmonary embolism Surg Gynecol Obstet 128 27 1969
15 Little J M and Lowenthal J Factors contributing to a lowered mortality from pulmonary embolism Surg Gynecol Obstet 127 777 1968
16 Gurewich V Thomas D P and Rabinov K R Pulmonary embolism after ligation of the inferior vena cava N Engl J Med 274 1350 1966
17 Barritt D W and Jordan S C Anticoagulant drugs in the treatment of pulmonary embolism Lancet 1 1309 1960

Table I Statistical analysis of the data–CW AMVL (LV) – CW PAR (DIA)

	Third ICS supine	*Fourth ICS Supine*	*Third ICS left lateral*	*Fourth ICS left lateral*
Mean (mm)	+ 1 94	+ 0 17	+ 6 81	+ 2 90
Standard deviation (mm)	± 5 48	± 5 20	± 5 08	± 6 21
Standard error (mm)	± 0 98	± 0 96	± 0 91	± 1 15
Range (mm)	−10 to +1?	−10 to +10	−2 to +14	−13 to +14
No of subjects	31	29	31	29
P value†	P > 0 05	P > 0 05	P < 0 01	P > 0 05

See F g 1 f definition of t rms.
†P alue refers to th statistical differe ces between the p ired me rements of depth from chest wall to AMVL (LV) and from chest wall to PAR (DIA) from the in i dual interspace nd patient position

Table II Statistical analysis of the data–CW AMVL (LA) – CW PAR (DIA)*

	Third ICS supine	*Fourth ICS supine*	*Third ICS left lateral*	*Fourth ICS left lateral*
Mean (mm)	−0 40	−2 1?	+ 5 6?	+ 1 93
Standard deviation (mm)	± 5 08	± 5 08	± 4 79	± 5 30
Standard error (mm)	± 0 93	± 0 91	± 0 86	± 1 02
Range (mm)	−11 to +9	−11 to +10	−2 to +14	−13 to +9
No of subjects	30	31	31	27
P value†	P > 0 05	P > 0 05	P < 0 01	P > 0 05

See F g 1 f r d fin tio of t rms.
†I lue ref rs to the t tist al differen es between th pa red measurements of d pth from chest wall to AMVL (LV) and fr m chest wall to PAR (DIA) from th indi idual int rspace a d patient positio

AMVL and the PAR when measured in each of the four recording positions An appreciation of the distribution of these differences is important to the echocardiographer in assessing aortic mitral valve continuity

Table I lists the mean range standard deviation standard error P value and number of subjects for the CW AMVL (LV) –CW PAR (DIA) parameter in each of the four positions Table II lists similar measurements for the CW AMVL (LA) –CW PAR (DIA) parameter Table III presents the per cent of scores in which the difference between the depth of the AMVL in the left ventricular region of the PAR at end diastole is less than +8 mm +9 mm and +10 mm or greater than −8 mm −9 mm and −10 mm Table IV presents similar data for the difference in the depth of the AMVL in the left atrial region and the PAR at end diastole Figs 2 and 3 are graphic representations of the distributions of differences in the parameters measured

Discussion

According to several authors the distance from the chest wall transducer echoes (CW) to the closed position (c point) of the anterior mitral valve leaflet (CW AMVL) is equal to the distance from the chest wall transducer echoes to the most posterior excursion of the posterior aortic root at end diastole CW PAR (DIA)

Our data show that there is no statistically significant difference (defined as $p < 0\ 01$) in the depth of the PAR at end diastole and the closing point of the AMVL (recorded in the LA or LV regions) when measured with respect to the chest wall transducer echoes in three of the four recording positions (the third and fourth ICS in the supine and the fourth ICS in the left lateral positions) The difference was however significant for the third ICS in the left lateral position

In Table I however it is apparent that there are moderate variations in the results when measuring from different positions Since all echocardiographic distances are measured with respect to the ultrasound transducer a change in position of the transducer from one interspace to another alters the orientation of cardiac structures and their distances from the transducer The effect of transducer position upon measured intracardiac dimensions is the most likely explanation for the unexpected results observed in the

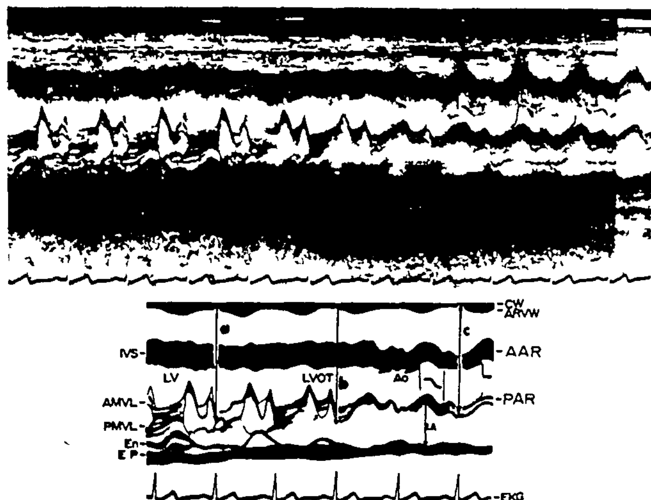


Fig 1 Top an actual M mode scan from the mitral valve with the left ventricular wall posteriorly to the ascending aorta Bottom a schematic diagram of a portion of the actual echogram Arrow *a* is the distance from the chest wall echoes to the closing point of the mitral valve in the left ventricular area Arrow *b* is the distance from the chest wall echoes to the closing point of the mitral valve in the left atrial area Arrow *c* is the distance from the chest wall echoes to the posterior aortic wall *CW* Chest wall *ARVW* anterior right ventricular wall *AAR* anterior aortic wall *PAR* posterior aortic wall *LA* left atrium *LVOT* left ventricular outflow tract *Ao* aorta *IVS* interventricular septum *AMVL* anterior mitral valve leaflet *PMVL* posterior mitral valve leaflet *En* endocardium *E P* epi pericardium

the appropriate situations The M mode speed was 25 mm per second and the strip recorder speed was 50 mm per second A water soluble gel was used to ensure an airtight seal between the transducer and the chest wall

Results

All 39 individuals were studied in all four positions yielding 156 echocardiograms In analyzing the CW AMVL (LV) −CW PAR (DIA) parameter, both the AMVL and the PAR were located in 120 recording positions Technically unsatisfactory recordings were obtained with the following incidence eight recordings in the third intercostal space (ICS) supine position 10 recordings in the fourth ICS supine position eight recordings in the third ICS left lateral position and 10 recordings in the fourth ICS left lateral positions Measurements from these records were not included in the study

In analyzing the CW AMVL (LA) −CW PAR (DIA) parameter both the AMVL and the PAR were located in 119 studies These technically unsatisfactory tracings were as follows nine recordings in the third ICS supine position, eight recordings in the fourth ICS supine position eight recordings in the third ICS left lateral position and 12 recordings in the fourth left lateral position These were also not included in the study

In all cases the AMVL was observed to be echocardiographically continuous with the PAR In several recordings however the two structures did not lie at the same echocardiographic depth with respect to the transducer–chest wall echoes Analysis of our data reveals that there is considerable variability in the relative depths of the

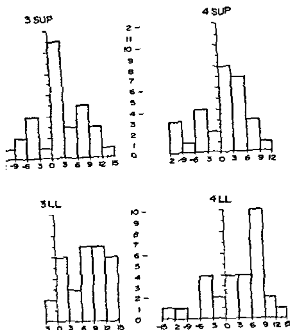


Fig 2 Bar graph representation of the distribution of scores from Table I The abscissa depicts the number of millim ters of difference the ordinate depicts the number of scores within that range

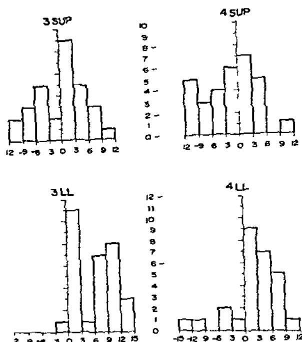


Fig 3 Bar graph representation of the distribution of scores from Table II The abscissa depicts the number of millimeters of difference the ordinate represents the number of scores within that range

(either third or fourth ICS in the supine position) These authors did not indicate whether they measured the AMVL in the left atrial or left ventricular area and neither author presented a statistical analysis of their data

With the recent advances in echocardiography the importance of establishing the presence of mitral semilunar valve continuity has become increasingly important in differentiating between various types of cyanotic congenital heart disease (e g tetralogy of Fallot and double outlet right ventricle) The term mitral semilunar valve continuity however actually describes the normal anatomical relationship (e g the fibrous continuity of the intervalvular fibrosa between the mitral and aortic valves which is uninterrupted by conal muscle) What is actually noted on single crystal echocardiography in the absence of the normal relationship between the posterior great vessel and the mitral valve should perhaps be referred to as mitral semilunar valve displacement Mitral semilunar displacement is not an easy sign to demonstrate echocardiographically and complete reliance cannot be placed on it because it is not dependent on anatomic discontinuity Due to variability in technique it can be produced in mitral regurgitation endocardial cushion defect and left ventricular enlargement when there is no anatomic discontinuity particularly when the transducer is held high on the chest wall Moreover variation in right and left orientation of the transducer on the chest wall will create continuity when it does not exist anatomically due to lateral resolution problems

It is hoped that this study of normal adult subjects will serve as a foundation for a more meaningful understanding of the mitral semilunar valve relationship

Summary

A prospective echocardiographic study of 39 healthy adults with no history of heart disease was conducted to investigate the relationship between the anterior mitral valve leaflet (AMVL) and the posterior aortic root (PAR) The difference between the echocardiographic depth of the AMVL and the depth of the PAR with respect to the chest wall (CW) echoes was measured from both the third and fourth intercostal spaces in both the supine and left lateral positions The results indicate that there were no statistically significant differences between the two depths in three of the four measuring position postures However the best correlation between the depth of the AMVL and the PAR was obtained in the

Table III Differences—CW AMVL (LV) – CW PAR (DIA)*

	Third ICS supine (%)	Fourth ICS supine (%)	Third ICS left lateral (%)	Fourth ICS left lateral (%)
– 8 mm	97	90	100	93
– 9 mm	97	90	100	93
– 10 mm	97	93	100	93
+ 8 mm	81	90	52	76
+ 9 mm	87	97	58	90
+ 10 mm	90	97	61	93

This table demonstrates the per cent of scores in which the differences between the depth of the AMVL in the LV region and the PAR at end diastole is less than + 8 mm + 9 mm and + 10 mm or greater than – 8 mm – 9 mm or – 10 mm See Fig 1 for a definition of terms

Table IV Differences—CW AMVL (LA) – CW PAR (DIA)*

	Third ICS supine (%)	Fourth ICS supine (%)	Third ICS left lateral (%)	Fou[rth ICS left] late[ral] (%
– 8 mm	93	81	100	9
– 9 mm	93	84	100	9
– 10 mm	97	90	100	9C
+ 8 mm	93	97	58	81
+ 9 mm	97	97	65	96
+ 10 mm	100	97	71	100

This table demonstrates the per cent of scores in which the diff between the depth of the AMVL in the LA region and the PAR a diastole is less than + 8 mm + 9 mm and + 10 mm and – 8 mm – 9 mm and – 10 mm See Fig 1 for a definition of

third left lateral position From this position the differences between the CW AMVL (LV) and the CW PAR (DIA) and the differences between the CW AMVL (LA) –CW PAR (DIA) parameter were statistically significant ($p < 0.01$) (Tables I and II) The mean ± standard deviation (standard error) for the former parameter was found to be 6 81 ± 5 08 (± 0 91 mm) and 5 65 ± 4 79 (± 86 mm) for the latter Both of these values were substantially greater than comparable measurements from the other three recording positions

In Tables III and IV are listed the per cent of scores in which the difference between the AMVL and the PAR depths is less than +8 mm +9 mm and +10 mm or greater than –8 mm –9 mm and –10 mm The c point of the AMVL in both the LA and the LV regions and the PAR at end diastole were within 10 mm of each other at least 90 per cent of the time except when recording in the third intercostal space (ICS) left lateral position Hence a difference greater than 10 mm in the third and fourth ICS supine positions or the fourth left lateral position would be suggestive of mitral aortic discontinuity It should be emphasized that all of these values were derived from a study of healthy adults whose ages ranged from 19 to 47 and that data from this study are not necessarily applicable to other age groups

In Figs 2 and 3 the distribution of scores we obtained in analyzing the CW AMVL (LV) –CW PAR (DIA) and CW AMVL (LA) –CW PAR (DIA) parameters are represented in a graphic form In analyzing these graphs it is evident that in the third and fourth ICS and the fourth ICS left lateral positions differences between the depths of the c po the AMVL and the PAR at end diastole f approximately a normal distribution Howe the measurements in the third left lateral posit are skewed to the right indicating a variance from the zero difference predicted the literature

Due to the possible difficulty in eval mitral semilunar valve continuity in the th ICS left lateral position we recommend t mitral semilunar valve continuity be determi in at least two of the following three positi the third or fourth ICS supine or fourth ICS degree left lateral In addition we conclude t mitral semilunar valve continuity is present if t difference in the echocardiographically measur depth of the c point of the AMVL and the PAR end diastole is less than 10 mm since 90 per c of our 120 valid studies were within this r This conclusion was valid whether the AMV was measured in the left atrial or in left ve ular region

The best published echocardiographic st of mitral semilunar valve continuity to date done by Chesler[6] and Strunk[13] and their workers Chesler studied 13 normal childr ranging in age from 3 months to 9 years detected no difference in the depth of the PA and the AMVL at end diastole with respect to chest wall transducer echoes Strunk found e tially similar results in a study of 30 subjects[13] In both of these studies the norm subjects were examined in only one interspac

Inhibition of a ventricular synchronous pacemaker

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Noncompetitive ventricular synchronous pacemakers (VVT) have been available since 1965.[2] The characteristics of their operation have been well delineated and understood.[3] The recent appearance of a new variety of ventricular synchronous pacer of different mode of operation than those previously used may lead to misinterpretation of the ECG and a diagnosis of pacer malfunction.

Early and most presently available VVT pulse generators (such as Cordis Ectocor)* have had a single fixed pulse to pulse interval (interval in milliseconds is the mathematical *reciprocal of* rate) divided into two portions a *total refractory period* of 300 to 400 msec following sensing of a QRS complex or emission of a stimulus followed by a *sensitive period* the duration of which is dependent on the pulse interval. If the pacemaker automatic rate is 70 per minute the pulse to pulse interval will be 857 msec the refractory period 400 msec and the sensitive period 460 msec. Slower or more rapid rates will have correspondingly longer or shorter sensitive periods as the refractory period is fixed. Any QRS complex or other electrical signal during the sensitive period produces a pacemaker stimulus. The generator cannot be inhibited under any circumstances.

The Cordis Omni Ectocor operates quite differently. It has a *refractory* and two *sensitive periods* one during which the generator is inhibited.[5] The pulse to pulse interval is noninvasively variable to produce six different rates 60 65 70 80 90 and 100 per minute though for reasons of the possibility of competition of a stimulus and a T wave in the presence of a short refractory period use of the 90 and 100 per minute rates is discouraged by the manufacturer. Those two rates can be used as they have been by the author but with caution and then largely for atrial pacing where ventricular T wave competition does not occur (Fig 1).

The refractory and sensitive periods of the Omni Ectocor pulse to pulse interval are further subdivided—the *refractory* into an *absolute refractory* and a *noise sampling* period the sensitive into a short *sensitive inhibited (S I)* and a longer *sensitive synchronous (S S)* portion. The pulse to pulse interval and its *four* subdivisions have fixed proportions but none is of fixed duration. As all generator output parameters vary with rate the impulse duration too varies as a function of the pulse to pulse interval[6] (Table I).

The pulse to pulse interval is subdivided into 512 bits the *refractory period* is 5/16 of 512 or 160 counts the refractory noise sampling period 1/16 of 512 or 32 *counts* the *sensitive inhibited period* 1/8 of 512 or 64 *counts* and the *sensitive synchronous period* 1/2 of 512 or 256 *counts*. Programming the pulse generator simply changes the duration of each bit changing the duration of each interval but not the relative *proportions*.

Clinical consequences

All earlier ventricular synchronous pacemakers could not be inhibited or slowed by an electrical stimuli.[7] Spontaneous QRS complexes in any combination (a QRS within the refractory *period*

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fourth ICS supine position The echocardiographic difference between the CW PAR and the CW AMVL was ≤ 8 mm in 90 per cent and ≤ 10 mm in 97 per cent of our subjects in the fourth ICS In the third intercostal space in the left lateral position however there was a statistically significant ($P < 0.01$) difference in the two dimensions In an individual subject, in any of the four possible positions however there were differences of up to 14 mm in the two depths The AMVL was found to be echocardiographically continuous with the PAR in all cases An understanding of the normal AMVL PAR relationship is becoming increasingly important especially in regard to the application of echocardiography to the diagnosis of congenital heart disease such as tetralogy of Fallot double outlet right ventricle and transposition of the great vessels and of mitral regurgitation

REFERENCES

1. Hurst J W Logue R B Schlant R C Wenger N K editors The heart New York 1974 McGraw Hill Book Company Inc p 28
2. Netter F The CIBA collection of medical illustrations—The heart Summit N J 1969 CIBA p 12
3. Grant J Grant s atlas of anatomy Baltimore 1972 The Williams & Wilkins Company p 454
4. Woodburne R Essentials of human anatomy New York 1969 Oxford University Press p 333
5. Hallermann F J Kincaid O W Ritter D G and Titus J L Mitral semilunar valve relationships in the angiography of cardiac malformations Radiology **94** 63 1970
6. Chesler E Joffee H S Beck W and Shrire Echocardiographic recognition of mitral semilunar discontinuity Circulation **43** 725 1971
7. Chesler E Joffe H S Beck W and Shrire Echocardiography in the diagnosis of congenital h disease Pediatr Clin North Am **18** 1163 1971
8. Tajik A Gau G Ritter D and Schattenbert Echocardiogram in tetralogy of Fallot Chest **64** 1973
9. Gramiak R Shah P and Kramer D Ultrasound cardiography Contrast studies in anatomy and funct Radiology **92** 939 1969
10. Gramiak R and Shah P Echocardiography of aortic root Invest Radiol **3** 356 1968
11. Gramiak R and Shah P Echocardiography of normal and diseased aortic valve Radiology **96** 1 1
12. Gramiak R and Shah P Cardiac ultrasonography review of current applications Radiol Clin North A **9** 469 1972
13. Strunk B Guss S Hicks R and Kotler M Echoc diographic recognition of the mitral valve posterior aor wall relationship Circulation **51** 594 1975
14. Morris D C Felner J M Schlant R C and Fran R H The echocardiographic diagnosis of tetralogy Fallot Am J Cardiol **36** 908 1975
15. French J W and Popp R Variability of di continui in double outlet right ventricle and truncus arterio Circulation **51** 848 1975
16. Goldberg S J Allen H D and Sahn D J Pediatr and adolescent echocardiography Chicago 1975 Ye Book Medical Publishers Inc pp 134 136
17. Sahn D J Allen H D and Goldberg S J Echocar diographic vs anatomical discontinuity Circulatio **53** 200 1976
18. Williams R G and Rudd M Echocardiographi features of endocardial cushion defect Circulation **49** 418 1974
19. Johnson M Holmes J H Spangler R D and Paton B C Echocardiographic diagnosis of mitral regurgita tion J Thorac Cardiovasc Surg **64** 922 1972

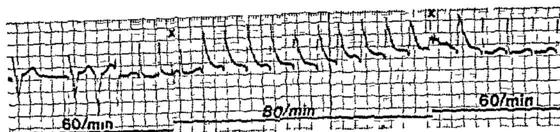


Fig 3 Variation in pacer automatic rate affects its response to a tachycardia Left Pacer automatic rate is 60 per minute and is inhibited by a tachycardia at a rate of 160 per minute Center Pacer programmed to automatic rate of 80 per minute is triggered by the same tachycardia Right Reprogrammed to 60 per minute the pacer is inhibited (X is the time of the programmer artifact)

Table I Omni Ectocor intervals

					Not recommended for ventricular pacing	
Rate per minute	60	65	70	80	90	100
Pulse duration (msec)	1.95	1.80	1.67	1.46	1.30	1.17
Total interval (msec)	1 000	923	857	750	667	600
Refractory (msec)	375	346	322	281	250	225
Noise sampling (msec)	63	58	54	47	42	37.5
Total sensitive (msec)	625	577	535	469	421	375
Sensitive inh. (msec)	125	115	107	94	84	75
Sensitive synch. (msec)	500	462	428	375	333	300
Inhibition interval (msec) for single stimulus	375 500	346 461	322 429	281 375	250 334	225 300
Inhibition rate for tachycardia per minute (upper and lower limits) (msec)	120 160	130 173	140 186	160 213	180 240	200 267

tional ventricular synchronous unit and that interference purposefully performed will allow demonstration of the underlying ventricular cardiac rhythm as is possible with ventricular inhibited units and unlike other ventricular synchronous units

Summary

Noncompetitive ventricular synchronous pacemakers (VVT) have been available since 1965 Most presently available and earlier models have a single fixed pulse to pulse interval divided into a total refractory period of 350 to 400 msec followed by a sensitive period During the refractory period the pacemaker will not respond to QRS complexes or electrical signals but a pacer stimulus will be produced during the sensitive period The generator cannot be inhibited under any circumstances The Cordis Omni Ectocor has a refractory period and two sensitive periods during one of which the generator is inhibited

Unlike other ventricular synchronous pacers the Omni Ectocor is capable of inhibition by single or multiple ventricular or other signals of slowing or increase of the stimulus formation rate which depends on the timing of the premature ventricular contractions and of inhibition by a run of ventricular tachycardia or by electromagnetic interference The rate of interference producing these effects is a function of the automatic rate to which the generator is programmed All of these factors must be considered for proper interpretation of the ECG

REFERENCES

1 Parsonnet V Furman S and Smyth N P D Implantable cardiac pacemakers status Report and resources guideline Circulation 50 A 21 1974
2 Parsonnet, V., Zucker I P Gilbert L and Myers G H Clinical use of an implantable standby pacemaker J A M A 196 04 1966
3 Furman S and Escher D J W Ventricular synchronous and demand pacing AM HEART J 76 445 1968
4 Sowton E Ventricular triggered pacemakers clinical experience Br Heart J 30 363 1968

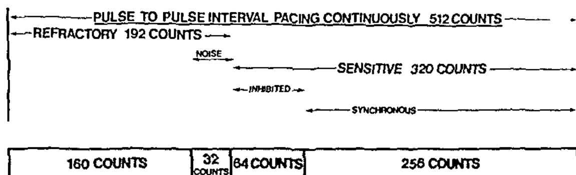


Fig 1 The pulse generator cycle is represented by the diagram no matter what the stimulation rate The duration *of each function the total interval or any part varies with the pulse generator rate The relative proportions* remain constant

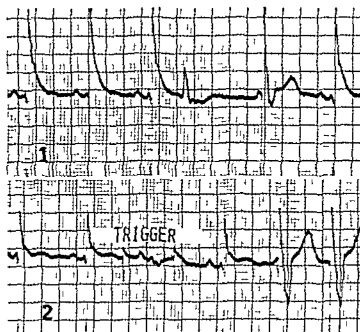


Fig 2 Inhibition of an Omni Ectocor is produced by a spontaneous contraction within the *sensitive inhibited* period (above) Transcutaneous stimulation at the appropriate rate inhibits the generator (below) Note also the pseudofusion beats and paced beats of customary ventricular synchronous (VVT) pacer function

of 400 msec would be unsensed) could not inhibit the pulse generator,[8] though the generator might be unaffected go to an asynchronous mode be driven to the maximum synchronous rate or de velop an erratic rate

The Omni Ectocor offers two additional circumstances, that of inhibition and slowing *below* the predetermined automatic rate Both are based on *discrete stimuli falling into the sensitive inhibited* (S I) period recycling the unit and once again falling into the S I period For a generator set at a rate of 70 per minute the ' S I" period extends for 107 msec from 322 msec after a sensed QRS or the emission of a stimul to 429 msec after A premature ventricular c traction, i e, coupled at 322 to 429 msec will sensed inhibit and recycle the generator as if were ventricular inhibited (Fig 2) Similarly ventricular tachycardia of rate 140 to 186 v inhibit the generator as will discrete electri stimuli at a similar rate At other rates intervals exist which will inhibit for a single cy or continuously inhibit the generator (Table I) Electromagnetic interference detected during noise sampling' period drives the unit to asy chronous operation during the S I period inhibi it and during the S S period triggers the unit Consequently, a variety of responses are possible and may exist consecutively as the frequency of the EMI varies or fluctuates (Fig 3)

Conclusions

Unlike earlier ventricular synchronous pace makers that of the Omnicor series is capable of inhibition by single or multiple ventricular or interfering signals and of inhibition slowing or increase *of the stimulus formation* rate as a function of the timing of a premature ventricular contraction, a run of ventricular tachycardia or of *electromagnetic interference* The rate of interfer ence producing *various effects* is a function of the automatic rate in which the generator operates A synchronous response may be converted to inhib ited (as well as the reverse) by programming another automatic *rate Each of these factors* must be considered to allow proper interpretation of the ECG Two implications also exist One that electromagnetic interference between 2 and 2 7 times the automatic *rate will inhibit* the genera tor eliminating the absolute safety of the conven

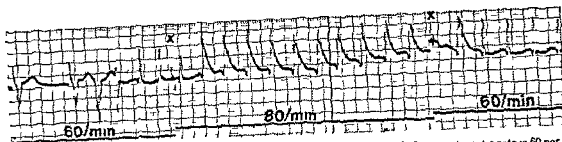


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per minute (upper and lower limits) (msec)	160	173	186	213	240	267

tional ventricular synchronous unit and that interference purposefully performed will allow demonstration of the underlying ventricular cardiac rhythm as is possible with ventricular inhibited units and unlike other ventricular synchronous units

Summary

Noncompetitive ventricular synchronous pacemakers (VVT) have been available since 1965 Most presently available and earlier models have a single fixed pulse to pulse interval divided into a total refractory period of 300 to 400 msec followed by a sensitive period During the refractory period the pacemaker will not respond to QRS complexes or electrical signals but a pacer stimulus will be produced during the sensitive period The generator cannot be inhibited under any circumstances The Cordis Omni Ectocor has a refractory period and two sensitive periods during one of which the generator is inhibited Unlike other ventricular synchronous pacers the Omni Ectocor is capable of inhibition by single or multiple ventricular or other signals of slowing or increase of the stimulus formation rate which depends on the timing of the premature ventricular contractions and of inhibition by a run of ventricular tachycardia or by electromagnetic interference The rate of interference producing these effects is a function of the automatic rate to which the generator is programmed All of these factors must be considered for proper interpretation of the ECG

REFERENCES

1 Parsonnet V Furman S and Smyth N P D Implantable cardiac pacemakers status Report and resources guideline Circulation 50 A 21 1974
2 Parsonnet V Zucker I R Gilbert L, and Myers, G H Clinical use of an implantable standby pacemaker J A M A 196 704 1966
3. Furman, S and Escher D J W Ventricular synchronous and demand pacing Am Heart J 76 445 1968
4 Sowton E Ventricular triggered pacemakers clinical experience Br Heart J 30 363 1968

5 Omni Ectocor programmable cardiac pacer (Manual) Cordis Corp Miami Fla 1973
6 Parsonnet V Cuddy T E Escher D J W Furman S Morse P Gilbert I and Zucker I R A permanent pacemaker capable of external non invasive programming Trans Am Soc Artif Intern Organs 29 224 1973
7 Furman S Parker B Krauthamer M and Escher D J W The influence of the electromagnetic envir ment on the performance of artificial cardiac pacem ers Ann Thorac Surg 6 90 1968
8 Smyth N P D Keshishian J M Hood O C H man A A Baker N R and Podolak E Effect of active magnetometer on permanently implanted pa makers J A M A 221 162 1972

Acute hemodynamic effects of an alpha- and beta receptor blocking agent (AH 5158) on the systemic and pulmonary circulation at rest and during exercise in hypertensive patients

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Adrenergic beta receptor blocking agents have increasingly been used and proved effective in the treatment of hypertensive disease during the last years Their blood pressure-lowering effect appears mainly if not entirely due to a decrease of cardiac output while the systemic vascular resistance has been shown to increase or to be unchanged

Constriction of the peripheral resistance vessels is mediated by adrenergic alpha receptors thus alpha receptor blocking agents should lower systemic blood pressure and have been shown to do so by decreasing peripheral vascular resistance as do other peripheral vasodilators i e hydralazine The pressure decrease induced by peripheral vasodilation however activates the baroreceptors homeostatic mechanisms thus causing an unwanted increase in heart rate and cardiac output

Studies in both the experimental animal and man [6] have shown that the homeostatic reflex mechanism elicited by peripheral vasodilation can be efficiently counteracted by the simultaneous administration of a beta receptor blocking agent An agent combining the properties of efficiently blocking both the beta 1 receptors in the heart and the alpha receptors of the resistance vessels can be anticipated to lower blood pressure by decreasing not only cardiac output but even the peripheral vascular resistance and would thus represent a particularly attractive antihypertensive agent from the hemodynamic point of view Using the combination of the beta receptor antagonist oxprenolol and the alpha receptor antagonist phentolamine Majid and associates[7] not only demonstrated this pattern of hemodynamic adaptation actually to occur at least in the acute experiment but they also showed that the combination had a more potent antihypertensive effect than each drug alone

The recently developed agent AH 5158 (Allen & Hanburys Research Ltd England) has been shown to be a competitive adrenergic blocking agent at both beta and alpha sites in both the experimental animal[8] and in man [9, 11] In the experimental animal it is 5 to 18 times less potent than propranolol in blocking beta receptors and 2 to 7 times less potent than phentolamine in blocking alpha receptors [8] In man the relative potencies of the alpha and beta receptor blocking properties are approximately 1 3 hence the compound has relatively less alpha than beta receptor blocking effects Like propranolol it is unselective with respect to beta receptors and lacks intrinsic sympathomimetic properties

The present study reports the acute hemodynamic effects of intravenously administered AH 5158 on the systemic and the pulmonary circulation during rest in both supine and upright positions and during exercise in patients with essential hypertension

Patients

Thirteen hypertensive patients 12 men and one woman mean age 52 0 ± 6 3 range 37 0 to 57 2 years who were referred to the department for investigation gave their informed consent to participate in this study In five hypertension

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Table I Patient data†

	No	Mean	SD	Range
Age (yr)	13	52 0	6 3	37 0–57 2
Length (cm)	13	173	10	153–185
Weight (Kg)	13	82 2	12 6	58–107
Blood vol (L)	13	*6 18*	*1 31*	*3 74–8 59*
THb (Gm)	13	807	226	429–1 044
Heart vol (ml)	13	1 027	280	670–1 480
HV/THb	13	1 30	0 25	0 99–1 73
Total work (k p m /min)	10	10 230	2 965	6 300–15 600
Renin activity (ng /ml)	12	2 95	2 48	1 14–8 46

†THb Total amount of hemoglobin HV heart volume total work as determined during ergometer exercise test prior to the hemodynamic examination

had been recently discovered and antihypertensive treatment had been initiated in one of these Eight patients had suffered from hypertension for between 1 and 14 years and all but one had been receiving antihypertensive treatment In all patients, however, all antihypertensive therapy had been discontinued at least 6 weeks prior to the hemodynamic examination Blood pressures when measured by the Riva Rocci cuff method ranged between 155/115 and 240/140 mm Hg at rest and 220/120 and 290/150 mm Hg during exercise

The clinical evaluation indicated that all had essential hypertension blood counts, serum electrolytes serum creatinine liver and renal function tests were normal Fundoscopic examination revealed no abnormality in one subject 11 had non exudative Grade 1 to 2 hypertensive changes one had Grade 3 exudative changes None had evidence of ischemic heart disease as evaluated by exercise electrocardiogram (ECG) (maximal work load between 600 and 1,200 kpm per minute) or of significant cardiac enlargement (relative heart volume 521 ± 117, range 350 to 700 ml per square meter of body surface area) Chest radiographs and spirometry gave no indication of lung disease Some relevant patient data including blood volume heart volume total amount of hemoglobin, and renin activity (in blood sampled immediately after exercise) are given in Table I

Methods

Prior to the hemodynamic study all the patients underwent a clinical examination including blood and urine analysis, an isotope renogram determination of blood volume by means of radioiodinated (' I) human serum albu (RIHSA) and of heart volume[1] and a number cardiopulmonary function tests ECG and pressure recording at rest in the supine upright position an exercise test with simul neous ECG and blood pressure recording a spirometric determination of lung volumes lation capacity, and gas distribution

Hemodynamic investigation were studied at rest in both the supine and upright positions and during steady state cise at two different work loads in the position on an electrically braked bicycle er eter as previously described[13] Both the static test and exercise on each work load for 6 minutes Work loads were 358 ± 81 (W_1) 723 ± 159 k p m per minute (W_2), W_2 corr sponding to about 70 to 80 per cent of patient's maximal O uptake

Having fasted overnight, the patients came the laboratory at about 8 A M Polyvinyl ters were inserted percutaneously[14] in a brach artery and in an antecubital vein, the tip of vein catheter was then placed into the pulmonary artery with the use of a spiral gu wire and fluoroscopy Twenty minutes allowed to elapse before the first (predrug) seri of measurements was started

On completion of the predrug study and after 15 minutes rest 5 ml (50 mg) of AH 5158 were administered intravenously over 5 minutes Arterial blood pressure was continuously corded from the beginning of injection until 30 minutes after the end of injection at which the second (postdrug) series of measurements wa taken under exactly identical conditions a during the predrug series

Blood pressures were recorded by means of an Elema 82 multichannel direct recorder using the Elema strain gauge transducers, together with the ECG In the supine position the midaxillary line, in the erect and sitting position the sternal angle was taken as zero pressure levels Pressure recordings were made after 4 minutes standing and exercise respectively

Cardiac output was determined according to the direct Fick principle Oxygen uptake was measured with the Douglas bag technique Expired air was collected during 5 minutes at rest in the supine and during 3 minutes at rest in the erect posture and during exercise starting 3 minutes after the onset of standing and exercise

Table II Means standard deviations (S D) and ranges of blood pressures and vascular resistances before and their mean ($\bar{D}$) and percentage ($\bar{D}$ %) changes after intravenous administration of 50 mg of AH 5158 at rest in the supine (R) and the upright (O) position and during exercise at two different work loads (W_1 and W)

	Mean	S D	Range	$\bar{D}$	$\bar{D}$ %
Brachial artery					
Systolic pressure					
R	1/4	3?	144 ?4/	−33	−19 0
O	1/9	35	148 247	−60	−33 5
W	20?	34	157 61	−61	−30 2
W	?41	34	177 294	−85	−35 3
Diastolic pressure					
R	97	15	87 115	−14	−14 4
O	108	19	88-1?3	−35	−3? 4
W	101	16	87 126	−?4	−23 8
W	113	24	85 144	−36	−31 9
Mean pressure					
R	1 6	18	112 144	−2?	−17 5
O	136	?3	116-16	−42	−30 9
W	143	?0	106-165	−40	−28 0
W	163	28	131 ?09	−5?	−31 9
Pulmonary artery (n = 12)					
Systolic pressure					
R	?3	/	9 36	−4	−17 4
O	19	6	13-31	−4	−21 1
W	31	7	21 4?	−3	−9 7
W	39	10	19 58	1	? 6
Diastolic pressure					
R	4 3	3 6	1 9	−1 4	−3? 6
O	8	2.8	−3 6	−0 8	−?8 4
W	7.9	3 3	3-14	0 7	8 9
W	13 3	6 5	3-?7	? 1	15 8
Mean pressure					
R	1? 3	4 4	6-?0	−2 3	−18 7
O	8	4 1	0-14	−1 5	−17 ?
W	16 8	5 9	10-?5	0 7	4?
W	23 9	8 5	11 38	2 ?	9 ?
SVR I					
R	48.?	1? 1	36 6-65 5	−5 2	−10 8
O	58 9	15 4	40 7 8? 0	−10 3	−17 5
W	3	6 3	14 9 38 6	−5 1	−?0 2
PVR I					
R	3 0	1 ?	1 1 4 5	−0 4	−13 3
O	2 6	1 3	1 1 5 1	0 2	7 7
W	1 6	0 /	0 8-?6	0 3	18 8

p < 0 05 p < 0 01 p < 0 001

respectively Arterial and mixed venous blood samples were taken simultaneously during the collection of expired air Because of the occurrence of marked postural hypotension the orthostatic test had to be shortened in two instances two patients had to be examined in the sitting rather than in the standing position

Table III Means standard deviations (S D) and ranges of some hemodynamic variables before and their mean ($\bar{D}$) and percentage ($\bar{D}$ %) changes after intravenous administration of 50 mg of AH 5158 at rest in the supine (R) and upright (O) position and during exercise at work load W_2 (723 ± 159 k p m /min)

	Mean	SD	Range	$\bar{D}$	$\bar{D}$ %
Heart rate					
R	73	8	60-84	−3	−4 1
O	87	15	60-104	−14	−16 1
W	146	?3	90-1?4	−37	−25 3
V_{O_2} (ml /min)					
R	269	48	219 375	−6	−2 2
O	351	79	233-513	−28	−8 0
W	1 7/6	290	1 006-? 117	−118	−6 6
AV_{O_2} diff (mL/L)					
R	51	12	30-68	2	3 9
O	75	10	54 90	8	10 7
W	138	13	113-162	17	12 3
C O (L /min)					
R	5 49	1 45	3 86-8 87	−0.50	−9 1
O	4 77	1 34	3 38-7 16	−0 87	−18 2
W	12 94	? 12	8.89 15 45	−2.11	−16 4
C I (L /min /M²)					
R	2.86	0 98	1 76-4 85	−0 29	−10 1
O	2.46	0 66	1 67 3 2?	−0 46	−18 ?
W	6 0	1.30	4 56-9 47	−1 11	−16 6
SV (mL)					
R	5	19	5? 106	0	0
O	58	23	32 10?	−2	−3 5
W	95	26	57 109	11	11 6

p < 0 05 p < 0 01 p < 0 001

Calculations The systemic (peripheral) vascular resistance index (SVRI) and the pulmonary vascular resistance index (PVRI) were calculated according to the equations

$$\text{SVRI} = \frac{\overline{P}_{BA} - \overline{P}_{RA}}{CI}$$

$$\text{and PVRI} = \frac{\overline{P}_{PA} - \overline{P}_{d\ \ PA}}{CI}$$

where $\overline{P}_{BA}$ $\overline{P}_{RA}$ and $\overline{P}_{PA}$ are the mean pressures in the brachial artery right atrium (resting value) and pulmonary artery respectively $\overline{P}_{d\ PA}$ the diastolic pressure in the pulmonary artery and CI the cardiac index It is well established[15] that in the absence of significant pulmonary hypertension the pulmonary artery diastolic pressure reflects the pulmonary wedge pressure

Dead space was calculated from Bohr s equation and the alveolar O tensions from the

alveolar gas equation, assuming arterial Pco_2 to equal mean alveolar Pco [16] This assumption appears justified in view of the very low anatomic right to left shunts present in these patients

Blood and gas analyses The volume of expired air was measured in a gasometer, O_2 and CO were determined according to Scholander,[17] the O_2 saturation and the hemoglobin concentration with a spectrophotometric method[18] using a Beckman B photometer, pH Po and Pco_2 were measured with microelectrodes using Radiometer s PMH 72, lactic acid was determined enzymatically [19] Blood gas analyses were performed within 30 minutes after sampling Methodological details, including the analytical accuracy, are given elsewhere [0]

Statistical methods Current statistical methods were used for calculation of standard deviations (S D) mean differences ($\overline{D}$) and t analysis [1] Comparison of data obtained before and after the administration of AH 5158 was always based on paired samples

Results

Mean values and standard deviations of some relevant hemodynamic parameters as measured prior to, as well as the changes observed after the administration of AH 5158 are given in Tables II and III

The pre treatment average *systemic blood pressure* was 174/97 (mean 125) mm Hg at rest in the supine and 179/108 (mean 136) mm Hg in the upright position It increased to 241/113 (mean 163) mm Hg during exercise (W_2) The administration of AH 5158 resulted in a marked (by 14 to 35 per cent) and statistically significant ($p < 0\ 001$) reduction of blood pressures under all conditions, the effect being most pronounced in the upright position and during exercise Systolic mean, and diastolic pressures were similarily affected

Blood pressures in the pulmonary circulation were within normal limits both before and after the administration of AH 5158 At rest in the supine and the upright position AH 5158 resulted in a statistically significant decrease (between 17 and 21 per cent) of the systolic and mean pressure During exercise pressures were not significantly affected

The *heart rate* was significantly reduced at rest in the upright position (by 16 per cent $p < 0\ 01$) and particularly during exercise (by 25 per cent $p < 0\ 001$) but not at rest in the supine position

Oxygen uptake (Vo_2) was slightly decreased ($p < 0\ 05$) during exercise ventilation (V_E) was not affected

Mean cardiac output was 9 per cent lower at rest in the supine position but this change was not statistically significant It was significantly lower in the erect posture (18 per cent, $p < 0\ 05$) and during exercise (16 per cent $p < 0\ 001$) This decrease was entirely due to a decrease in heart rate, since *stroke volume* was not affected at rest, and during exercise increased by 12 per cent ($p < 0\ 05$) The *arterial-mixed venous oxygen difference* was increased in the erect posture and during exercise

The mean *systemic vascular resistance* index was 11 per cent lower at rest in the supine position, but this change was not statistically significant It was significantly lower in the erect posture (17 per cent $p < 0\ 05$) and during exercise (20 per cent $p < 0\ 01$) The mean *pulmonary vascular resistance* index was unchanged at rest but slightly higher ($p < 0\ 05$) during exercise

Table IV summarizes the most relevant data concerning *pulmonary ventilation gas exchange* and *acid base balance* Only minimal changes occurred after AH 5158 at rest in the supine position tidal volume (V_T) and alveolar ventilation (V_A) were slightly increased and the respiratory exchange ratio (R) slightly decreased No changes occurred during rest in the erect posture During exercise (W) tidal volume (V_T) and oxygen uptake (Vo_2) were slightly lower, while the respiratory rate and the alveolar ventilation in relation to cardiac output ($V_A/\dot{Q}$) were slightly higher Not any significant change was observed concerning the alveolar–arterial oxygen tension difference arterial blood gases acid base balance or arterial lactate concentrations

Discussion

AH 5158 administered intravenously in a dose of 50 mg had a marked antihypertensive effect inducing a fall in systemic systolic diastolic and mean pressures by between 14 per cent (diastolic pressure at rest in the supine position) and 35 per cent (systolic pressure during exercise) at rest both in the supine and upright position and during exercise The main pressure fall occurred within the first 10 minutes following the onset of injection

Table IV Means and standard deviations (S D) of some variables concerning pulmonary ventilation gas exchange and acid base balance before and their mean changes ($\bar{D}$) after intravenous administration of 50 mg of AH 5158 at rest in the supine and upright position and during exercise at work load W_2 (723 ± 159 k p m /min)

	Rest supine			*Rest upright*			*Exercise W* (723 ± 159 k.p m /min)		
	Mean	*S D*	$\bar{D}$	*Mean*	*S D*	$\bar{D}$	*Mean*	*S.D*	$\bar{D}$
Resp rate (br /min)	14.8	2.4	1.0	17.5	3.9	1.4	23.0	4.9	3.5
V_T 1 BTPS	0.78	0.31	0.10	0.91	0.36	0	2.42	0.61	–0.3
V_E 1 BTPS	11.01	4.15	–0.64	15.31	5.00	0.14	54.67	13.95	0.21
V_O 1 STPD	0.24	0.05	–0.01	0.35	0 9	–0.03	1.78	0.29	–0.12
R	0.85	0.15	–0.06	0.81	0.13	0.04	0.93	0.09	0.04
V_E/V_O	41.4	14.5	–2.3	43.4	10.5	4.6	30.6	5.4	3.2
V_A 1 BTPS	6.19	2.82	–0.45	8.86	3.99	0.01	43.58	10.58	0.68
V_A/V_O	21.5	9.0	–1.4	23.3	7.8	2.2	25.6	6.2	2.6
V_D/V_T	38.7	7.2	0.2	38.6	9.4	–0.1	17.8	8.1	0.2
P_{A_O} Pa_O (mm Hg)	23.0	5.9	2.3	19.1	4.6	–0.1	24.5	8.1	–1.2
Pa_O (mm Hg)	87.0	10.6	–4.1	94.2	12.1	1.7	90.7	9.7	2.7
Pa_{CO} (mm Hg)	34.5	4.4	–0.3	30.4	4.3	0.3	34.1	3.5	–2.3
V_A/Q	1.20	0.67	–0.06	1.88	0.76	0.37	3.35	0.54	0.9
pH	7.45	0.06	–0.01	7.46	0.05	–0.01	7.37	0.03	–0.01
Stand bic (mMol /L)	24.0	2.3	–0.5	23.1	1.1	–0.6	21.4	4.4	–2.2
Lactate (mMol /L)	1.08	0.43	0.4	1.27	0.62	0.24	3.75	1.49	0.39
Lactate† (mMol /L)							4.07	1.22	0.59

†Val es 4 min a w
P < 0.05 p < 0.01

The mode of antihypertensive action was similar at rest and during exercise blood pressure was lowered by a reduction of both cardiac output and the systemic vascular resistance These effects were particularly evident in the upright position and during exercise During exercise the relative decrease of the vascular resistance was more important than that of cardiac output The reduction of cardiac output was entirely due to a decrease of heart rate and not of stroke volume during exercise stroke volume even increased by 12 per cent after AH 5158 ($p < 0.05$) These changes toward a slightly more hypokinetic circulation in the upright position and during exercise were accompanied by an increase of the arterial-mixed venous oxygen difference by 11 and 12 per cent during standing in the upright position ($p < 0.01$) and during exercise ($p < 0.001$) respectively

There are slight differences in the hemodynamic effects between different beta blockers due to the presence or lack of intrinsic sympathomimetic activity moreover the hemodynamic effect is somewhat dependent on the degree and the stage of the hypertensive disease Regardless of these minor differences the acute hemodynamic effect of parenteral administration of a beta adrenergic blocking agent consists principally in a reduction of cardiac output and an increase of systemic vascular resistance Cardiac output is reduced by a decrease of heart rate but also by a reduction of stroke volume The net result of this adaptation is a virtually unchanged or only slightly decreased arterial blood pressure The oxygen carrying capacity of the decreased circulating blood volume is maintained by a substantial increase of the arterial-mixed venous oxygen difference total oxygen uptake being unchanged

Due to the additional alpha receptor blocking properties the acute hemodynamic effect of AH 5158 is as could be anticipated significantly different from that of an agent which exclusively blocks the adrenergic beta receptors By blocking the (dilator) beta 2 receptors in the resistance vessels the beta receptor blockers increase the relative effect of the (constrictor) alpha receptors thus inducing an increase in systemic vascular resistance which inhibits the antihypertensive effect anticipated from the decrease of cardiac output The additonal alpha receptor blocking effect of AH 5158 inversely induces a decrease of

the systemic vascular resistance and probably even attenuates the cardiac output-lowering effect of the beta blocking component The alpha receptor blocking component, however also increases the probability of postural hypo tension to occur Four of the patients in this group actually experienced marked postural hypotension necessitating a minor modification or shortening of the investigation procedure in the erect posture

A *similar effect* on blood pressure and on systemic vascular resistance has been shown to occur after the acute administration of a periph eral vasodilator such as hydralazine[6] or phento lamine[7] when supplemented by a beta blocker On the other hand, clonidine an antihypertensive agent which mainly inhibits the sympathetic vasomotor center, has been shown to have hemo dynamic effects at rest and during exercise more similar to those of beta receptor blockers with out however increasing the systemic vascular resistance [5]

The effect of AH 5158 on the pulmonary circu lation is especially noteworthy at rest both in the supine and in the upright positions there was a reduction ($p < 0.01$) of systolic and mean pres sures while the changes of diastolic pressures under all conditions and of systolic and mean *pressures during exercise were inconsistent* De spite these hemodynamic effects on the pulmo nary circulation pulmonary ventilation was only minimally affected and intrapulmonary gas exchange and acid base balance were not at all affected

The pulmonary artery diastolic pressure has been shown (see Forsberg[11] and Koch unpub lished data) to reflect pulmonary wedge and thus left ventricular filling pressure in the absence of significant increase of pulmonary vascular resis tance The absence of any rise of the diastolic pressure at rest and during exercise clearly demonstrates that AH 5158 at least in the acute experiment and with the dose used lacks signifi cant negative inotropic effects on the left heart which is further suggested by the absence of any reduction in stroke volume on the contrary stroke volume increased by 12 per cent during exercise A similar reduction of pulmonary artery pressures has been shown to occur after cloni dine [5] whereas a rise has been reported for beta receptor blockers especially propranolol [2,3]

Due to its particular hemodynamic effects *comprising both a reduction* of cardiac output and especially of systemic vascular resistance without indication of significant negative inotrop ic cardiac action AH 5158 appears to be a partic ularly attractive antihypertensive drug at least in the management of acute hypertensive crisis It has already been shown that the antihypertensive effect persists during long term oral treatment (see Prichard and associates[11] and Koch unpub lished data) there are, however still no data available indicating that the favorable hemody namic pattern of adaptation induced by the intravenous administration of the drug does *persist during long term oral treatment* For the combination of oxprenolol plus hydralazine given orally for several months it has recently been shown that the vasodilator effect of hydralazine is largely overshadowed by the hemodynamic effects of the beta receptor antagonist It will thus be of considerable interest to determine the hemodynamic effects of AH 5158 after long term oral treatment

Summary

The acute hemodynamic effects of 50 mg of the alpha and beta receptor blocking agent AH 5158 administered intravenously on the systemic and pulmonary circulation were studied in 13 *hypertensive patients at rest in the supine and erect positions and during exercise with right heart and brachial artery catheterization*

AH 5158 induced a signficant fall of systemic blood pressures under all conditions whereas the pulmonary systolic and mean pressures were lower at rest and unaltered during exercise The left ventricular filling pressure largely remained unchanged

Blood pressure was lowered predominantly by a reduction in systemic vascular resistance to gether with a reduction in cardiac output These *effects were particularly* pronounced in the erect position and during exercise Cardiac output was lowered solely by the reduction of heart rate, stroke volume was unchanged or even increased The arterial-mixed venous oxygen *difference* increased in the erect position and during exer cise

The pattern of AH 5158 induced hemodynamic adaptation comprising a reduction of both vascular resistance and cardiac output without evidence of significant negative inotropic action offers a novel basis for treating *hypertension* with

single drug Its pharmacological and hemody namic profile suggests considerable potential in the treatment of hypertensive patients

REFERENCES

1 Simpson F O Beta adrenergic receptor blocking drugs in hypertension Drugs 7 85 1974
2 Werko L New treatment for hypertension Leading article Eur J Clin Pharmacol 3 61 1971
3 Majd P A Meeran M K Benaim M E Sharma B and Taylor S H Alpha and beta adrenergic receptor blockade in the treatment of hypertension Br Heart J 36 588 1974
4 Jonston C I Pathophysiological rationale for the use of vasodilators in hypertension Med J Aust Spec Suppl 1 3 1975
5 Brunner H Hedwall P R and Meier M Influence of adrenergic beta receptor blockade on the acute cardio vascular effects of hydralazine Br J Pharmacol 30 123 1967
6 Sannerstedt R Stenberg J Johnsson G and Werko L Hemodynamic interference of alprenolol with dihy dralazine in normal and hypertensive man Am J Cardiol 28 316 1971
7 Koch, G Hemodynamic adaptation at rest and during exercise to long term antihyperten sive treatment with the combination of a beta receptor blocking and vasodi lator agent Br Heart J in press
8 Farmer J B Kennedy I Levy G P and Marshall R J Pharmacology of AH 5158 a drug which blocks both alpha and beta adrenoreceptors Br J Pharmacol 45 660 19 2
9 Collier J G Dawnay N A H Nachev C H and Robinson B F Clinical investigation of an antagonist at alpha and beta adrenoreceptors—AH 5158 A Br J Pharmacol 44 286 1972
10 Richards D A Woodings E P Stephens M D B and Maconochie J G The effects of oral AH 5158 a combined alpha and beta adrenoreceptor antagonist in healthy volunteers Br J Clin Pharmacol 1 505 1974
11 Prichard B N C Thompson F O Boakes A J and Joekes A M Some haemodynamic effects of compound AH 5158 compared with propranolol propranolol plus hydralazine and diazoxide The use of AH 5158 in the treatment of hyperten sion Clin Sci Mol Med 48 9 19 5
12 Larsson H and Kjellberg S R Roentgenological heart volume determination with special regard to pulse rate and the position of the body Acta Radiol (Stockh) 29 159 1948
13 Jakobsson K A Koch G Levander Lindgren M and Michaelsson G Double blind trial with prenylamine (Segotin) in coronary insufficiency Acta Med Scand 180 196 1966
14 Koch G Simplified method for percutaneous arterial catheterisation Lancet 2 1166 1971
15 Forsberg S A Relations between the pressure in the pulmonary artery left atrium and left ventricle with special reference to events around the end of diastole Br Heart J 33 494 1971
16 Comroe J H Jr Forster R E Dubois A B Briscoe W H and Carlsen E The lung Clinical physiology and pulmonary function tests ed 2 Chicago 1967 Year Book Medical Publishers Inc
17 Scholander P F Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples, J Biol Chem 167 235 194
18 Holmgren A and Pernow B Spectophotometric measurement of oxygen saturation of blood in the deter mination of cardiac output A comparison with the Van Slyke method Scand J Clin Lab Invest 11 143 1959
19 Hohorst H J L-(+) lactate Determination with lactic dehydrogenase and D P N in Bergmeyer H U editor Methods of enzymatic analysis Verlag Chemie GmbH New York, 1963 Academic Press Inc
20 Koch G Lung function and acid base balance in the newborn infant Acta Paediatr Scand Suppl 181 1968
21 Snedecor G W Statistical methods ed 6 Ames, Iowa 1967 The Iowa State University Press
22 Johnsson G De Guzman M Bergman H and Sanner stedt, R The haemodynamic effects of alprenolol and propranolol at rest and during exercise in hypertensive patients Pharm Clin 2 34 1969
23 Taylor S H Majd P A Saxton C and Stoker J B Comparison of the circulatory effects of oxprenolol and propranolol in hypertensive patients *in* Simpson F O editor Beta adrenergic receptor blocking drugs Hor sham 1970
24 Sannerstedt R Selection of hypertensive patients for treatment with beta blockers alone or in combination *In* Schweizer W editor Beta blockers—present status and future prospects Berne 1974 Hans Huber Publishers
25 Koch G Hemodynamic effects of 2 (2 6-dichloropheny lamino) 2 imidazoline hydrochloride (St 155) at rest and during exercise with special respect to the pulmonary circulation Arzneim Forsch (Drug Res) 21 57 1971

the systemic vascular resistance and probably even attenuates the cardiac output-lowering effect of the beta blocking component The alpha receptor blocking component, however also increases the probability of postural hypotension to occur Four of the patients in this group actually experienced marked postural hypotension necessitating a minor modification or shortening of the investigation procedure in the erect posture

A similar effect on blood pressure and on systemic vascular resistance has been shown to occur after the acute administration of a peripheral vasodilator such as hydralazine[6] or phentolamine[7] when supplemented by a beta blocker On the other hand, clonidine an antihypertensive agent which mainly inhibits the sympathetic vasomotor center has been shown to have hemodynamic effects at rest and during exercise more similar to those of beta receptor blockers with out however, increasing the systemic vascular resistance [9]

The effect of AH 5158 on the pulmonary circulation is especially noteworthy at rest, both in the supine and in the upright positions, there was a reduction ($p < 0.01$) of systolic and mean pressures while the changes of diastolic pressures under all conditions and of systolic and mean pressures during exercise were inconsistent Despite these hemodynamic effects on the pulmonary circulation pulmonary ventilation was only minimally affected and intrapulmonary gas exchange and acid base balance were not at all affected

The pulmonary artery diastolic pressure has been shown (see Forsberg[10] and Koch, unpublished data) to reflect pulmonary wedge and thus left ventricular filling pressure in the absence of significant increase of pulmonary vascular resistance The absence of any rise of the diastolic pressure at rest and during exercise clearly demonstrates that AH 5158 at least in the acute experiment and with the dose used lacks significant negative inotropic effects on the left heart which is further suggested by the absence of any reduction in stroke volume, on the contrary stroke volume increased by 12 per cent during exercise A similar reduction of pulmonary artery pressures has been shown to occur after clonidine [9] whereas a rise has been reported for beta receptor blockers especially propranolol

Due to its particular hemodynamic effects comprising both a reduction of cardiac outp and especially of systemic vascular resistanc without indication of significant negative inotrop ic cardiac action AH 5158 appears to be a partic ularly attractive antihypertensive drug at leas in the management of acute hypertensive crisis I has already been shown that the antihypertensi effect persists during long term oral treatmer (see Prichard and associates[11] and Koch, unpub lished data), there are, however, still no dat available indicating that the favorable hemody namic pattern of adaptation induced by th intravenous administration of the drug doe persist during long term oral treatment For th combination of oxprenolol plus hydralazine give orally for several months it has recently bee shown that the vasodilator effect of hydralazin is largely overshadowed by the hemodynam effects of the beta receptor antagonist It wi thus be of considerable interest to determine th hemodynamic effects of AH 5158 after long ter oral treatment

Summary

The acute hemodynamic effects of 50 mg of the alpha and beta receptor blocking agent AH 5158 administered intravenously on the system and pulmonary circulation were studied in 1J hypertensive patients at rest in the supine and erect positions and during exercise with right heart and brachial artery catheterization

AH 5158 induced a signficant fall of systemic blood pressures under all conditions whereas the pulmonary systolic and mean pressures were lower at rest and unaltered during exercise The left ventricular filling pressure largely remained unchanged

Blood pressure was lowered predominantly by a reduction in systemic vascular resistance together with a reduction in cardiac output These effects were particularly pronounced in the erect position and during exercise Cardiac output was lowered solely by the reduction of heart rate stroke volume was unchanged or even increased The arterial-mixed venous oxygen difference increased in the erect position and during exercise

The pattern of AH 5158 induced hemodynamic adaptation comprising a reduction of both vascular resistance and cardiac output without evidence of significant negative inotropic action offers a novel basis for treating hypertension with

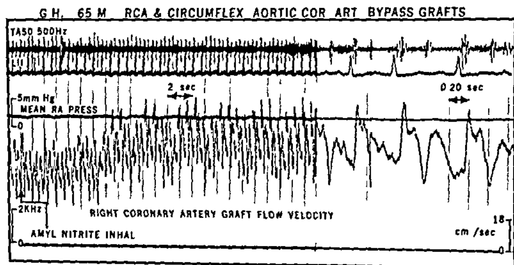


Fig 1 Simultaneously recorded tricuspid area (*TA*) phonocardiogram Lead II (*L II*) of the electrocardiogram mean right atrial (*RA*) pressure and aortic right coronary artery graft blood velocity in a 65 year-old man with coronary artery disease Amyl nitrite inhalation produces a rise in peak blood velocity Maximal bypass graft blood velocity is recorded 14 seconds after administration of the drug The right portion of the figure represents a continuous segment of the record at a faster paper speed

on a light beam oscillographic recorder (Electronics for Medicine Model DR 12) operated at various paper speeds

After obtaining a stable control record a crushed ampule containing 0 3 c c of amyl nitrite was held 1 inch from the patient s nostrils for 10 to 20 seconds The patients were carefully instructed to breathe the fumes at their normal rate and depth of respiration Aortocoronary blood velocity measurements were obtained continuously without catheter repositioning for periods up to 2 minutes

Results

Amyl nitrite inhalation produced an increase in heart rate and aortocoronary graft blood velocity in all subjects Phasic blood velocity augmentation was detected within 10 seconds after administration of the drug Maximal peak blood velocities were recorded between 8 and 60 seconds after the start of inhalation (Fig 1) The rise of peak aortocoronary bypass blood velocity ranged from 4 to 36 cm per second with a mean of 21 cm per second for the study group (control x peak blood velocity ± 1 S D = 25 ± 10 cm per second after amyl nitrite = 46 ± 14 cm per second P < 0 001) This represented an average 84 per cent increase of peak blood velocity induced by the drug (Fig 2) Both systolic and diastolic bypass graft blood velocities were augmented after amyl nitrite but the relative rise of the diastolic fraction was uniformly greater (Fig 3)

When the angiographic evaluation of saphenous vein graft and coronary arterial status was compared with the per cent increase of aortocoronary bypass blood velocity it was found that the two subjects with lowest relative rise of peak blood velocity after amyl nitrite had the poorest graft "run off In both patients peak bypass graft blood velocities increased by no more than 20 per cent (control blood velocities = 20 and 30 cm per second after amyl nitrite = 24 and 36 cm per second respectively)

Discussion

The data set forth in this study indicate that amyl nitrite enhances the velocity of blood as it flows into the aortocoronary saphenous vein bypass grafts of intact human subjects Such results must be considered in the light of investigations concerned with the influence of nitrites on native coronary arterial blood velocity In 1972[3] an average of 67 to 80 per cent increase of phasic coronary blood velocity was reported in conscious patients after amyl nitrite inhalation Simultaneous coronary arterial blood velocity and femoral arterial pressure recordings demonstrated that coronary blood velocity increased before the onset of amyl nitrite induced peripheral arterial hypotension This rise of coronary

Effects of amyl nitrite on phasic aortocoronary bypass graft blood velocity in man

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Recent study[1] from this laboratory has demonstrated the feasibility of measuring phasic instantaneous aortocoronary bypass graft blood velocity in conscious man by means of a Doppler flowmeter catheter During initial investigation with this technique it was noted that the inhalation of amyl nitrite produced a rise of peak aortocoronary bypass blood velocity in two subjects [1]

The purpose of this paper is to describe the influence of amyl nitrite administration on aortocoronary bypass graft blood velocity in a larger group of patients

Material and method

Twenty subjects with aortocoronary saphenous vein bypass grafts comprised the study group All patients had bypass graft procedures because of angina pectoris considered refractory to medical treatment with coronary vasodilators propranolol, and other medication The preoperative diagnosis of coronary artery disease was made on the basis of selective coronary arteriography There were 20 men whose ages ranged from 40 to 65 years with a mean of 52 years

All subjects underwent study by means of right and left heart catheterization along with selective coronary arterial and graft cineangiography after a postoperative period ranging from 1 month to 2 years After informed consent had been obtained studies were performed with patients in the nonsedated postabsorptive state in the supine position A right or left medial antecubital vein and brachial artery were exposed under local anesthesia with 1 per cent lidocaine Intracardiac pressures were measured with saline filled No 7 or 8 catheters connected to a Statham P23Db strain gauge Ostia of the aortocoronary grafts were identified by metal clips which had been affixed to the aorta at the graft origin during cardiac surgery

Aortocoronary graft blood velocity was measured by telemetry with a method which has been previously described in detail [1] The Doppler flowmeter catheter was advanced from the brachial artery to the ascending aorta under fluoroscopic control and its tip positioned at the origin but not within the lumen of the graft being studied When the catheter tip was maneuvered from the midaortic lumen to the origin of a graft there was an abrupt reduction of peak systolic blood velocity and an increase of peak diastolic blood velocity Careful withdrawal and repositioning of the catheter tip at the graft origin under fluoroscopic control resulted in identical and reproducible changes which have been demonstrated to characteristically represent bypass graft blood velocity [1] The anatomic distribution of grafts so studied was 10 patients, right coronary artery 9 patients left anterior descending coronary artery, 1 subject left circumflex coronary artery—thus providing a total of 20 graft blood velocity measurements

The analogue record of bypass graft blood velocity intracardiac pressures, and Lead II of the electrocardiogram were recorded on a multichannel tape recorder (Sanborn Model 3900) and

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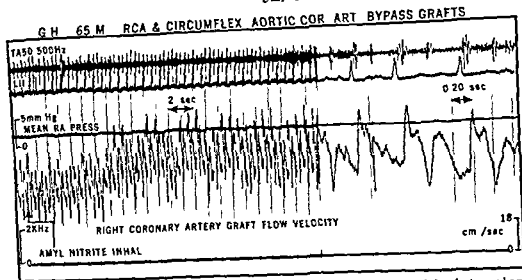


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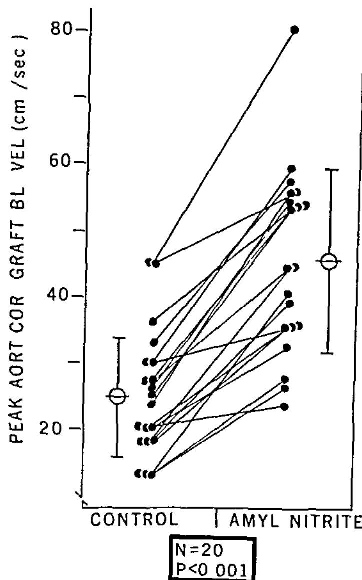


Fig 2 Measured values for peak aortocoronary bypass graft blood velocity in the study group during the control period and after inhalation of amyl nitrite There is a significant ($P < 0.001$) difference between values obtained prior to and after administration of the drug Mean values (± 1 S D) are indicated Amyl nitrite results in an average 84 per cent rise of blood velocity in 20 patients

blood velocity in patients given drugs with known vasodilating effects provided strong evidence that nitrites probably increase phasic coronary blood flow in man

No previous study has provided information regarding the influence of nitrites on phasic bypass graft blood velocity or volumetric flow in closed chest unanesthetized subjects Papaverine has been injected into autogenous aortocoronary bypass grafts at the time of operation thereby doubling electromagnetically measureable phasic patent graft flow [4, 5] The absence of this bypass graft blood flow augmentation has been correlated with ultimate graft occlusion Direct graft injection of nitroglycerin has been performed under similar open chest conditions resulting in a mean 54 per cent increase of phasic saphenous vein bypass blood flow This rise of volumetric graft blood flow generally occurred within 4 to 6 seconds after injection of the drug and lasted 30 to 40 seconds On the other hand intravenous administration of nitroglycerin during the same study effected an increase of graft blood flow in only a single subject It is difficult to assess the influence of peripherally administered drugs on anesthetized open chest patients directly following extracorporeal circulatory techniques

The Doppler flowmeter catheter utilized in this study measured phasic graft blood velocity and not volumetric flow [1] It is of interest, however that the dominant diastolic blood velocity fraction succeeded by a sharp systolic peak recorded in the patients described here resembled phasic aortocoronary graft blood flow patterns directly measured at the time of surgery during other experiments [7]

The results of this study do not prove that amyl nitrite evokes an increase of blood flow through the distal saphenous vein graft-coronary artery anastamosis The instantaneous characteristics of antegrade or retrograde systolic and diastolic blood velocities within the bypass graft of closed chest patients remain to be elucidated and may provide important data in this area Alternatively if the effects of amyl nitrite *observed here do indirectly represent increased* blood flow into the grafted coronary artery then the clinical implications are clear Under such conditions the bypass graft might permit greater delivery of coronary vasodilators to the distal coronary circulation thus favoring redistribution of blood flow perfusion in diseased or ischemic areas of the left ventricle

In conclusion, amyl nitrite inhalation produces a rise of phasic instantaneous aortocoronary bypass graft blood velocity suggesting increased myocardial blood flow in the intact human subject

Summary

With the use of a Doppler flowmeter catheter phasic instantaneous aortocoronary saphenous vein bypass graft blood velocity was continuously measured during the inhalation of amyl nitrite in 20 closed chest conscious subjects Administration of amyl nitrite augmented peak diastolic and systolic graft blood velocity within 10 seconds and maximal blood velocities were recorded between 8

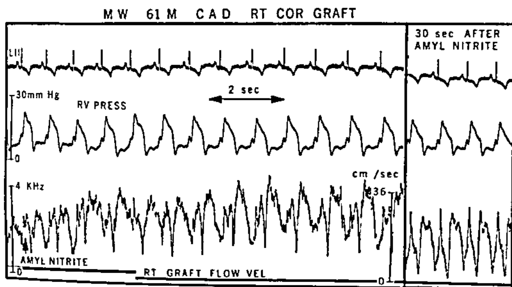


Fig 3 Simultaneously recorded Lead II (*L II*) of the electrocardiogram right ventricular (*RV*) pressure and phasic aortic right coronary artery bypass graft blood velocity in a 61 year-old man with coronary artery disease Amyl nitrite inhalation produces a rise in both systolic and diastolic blood velocity components yet there is a greater relative increase of the peak diastolic fraction

and 60 seconds after inhalation Control mean (± 1 SD) bypass graft blood velocity was 25 ± 10 cm per second and after amyl nitrite 46 ± 14 cm per second resulting in an average 84 per cent rise of blood velocity It is concluded that amyl nitrite increases aortocoronary bypass graft blood velocity suggesting a possible enhancement of blood flow to the distal native circulation in patients so operated upon

We would like to acknowledge the technical assistance of Carole Crevier Judy Norton Carol Graves R N Betty Jo Massey and Sydney Peebles.

REFERENCES

1 Benchimol A and Desser K B Measurement of phasic aortocornary bypass graft blood flow velocity in conscious man. Am. J Cardiol 32 895 1973
2 J hnson W D and Lepley D Jr Aggressive surgical approach to coronary disease J Thorac Cardiovasc Surg 59 128 1970
3 Benchimol A Desser K B and Gartlan J L. Effects of amyl nitrite on coronary arterial blood flow velocity in man Am J Cardiol 30 3_7 19/2
4 Grodin C M Meere C Castonguay Y R et al Blood flow through aorta to coronary artery bypass grafts and early postoperative patency Ann Thorac Surg 12 574 1971
5 Moran J M Chen P Y and Rheinlander H F Coronary hemodynamics following aorta-coronary by pass graft Arch Surg 103 539 19/1
6 Grodin C M Lepage G Castonguay Y R et al Aortocoronary bypass graft Initial blood flow through the graft and early postoperative patency Circulation 44 815 1971
7 Greenfield J C Jr Rembert J C., Young W G., Jr et al Studies of blood flow in aorta to-coronary venous bypass grafts in man J Clin Invest 51 2724 1972
8 Horwitz L D Gorlin R Taylor W J et al. Effects of nitroglycerin on regional myocardial blood flow in coronary artery disease J Clin. Invest 50 15/8 1971

Echocardiographic evaluation of septal motion in patients with artificial pacemakers Vectorcardiographic correlations

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Ventricular septal echocardiography (ECHO)[1] has proved to be valuable in the diagnosis of cardiomyopathies congenital heart diseases, and coronary artery disease and in the assessment of left ventricular function

Recently several reports [3] described abnormal septal motion in patients with left bundle branch block (LBBB)

This study was carried out to evaluate inter ventricular septal motion in patients with trans venous endocardial right ventricular pacemakers It was also designed to determine whether differ ences in septal motion could be explained by various patterns of cardiac activation in patients with clinical LBBB and in pacemaker induced LBBB

We were also interested in obvious practical implications resulting from identification of ECHO patterns of septal motion in patients with artificial pacemakers

Material and methods

Twenty one consecutive patients with transve nous endocardial right ventricular pacemakers and one patient with epicardial right ventricular pacemaker were studied by ECHO electrocardio gram (ECG), and vectocardiogram (VCG) (Frank system) The group consisted of 18 men and four women ranging in age from 21 to 86 years The clinical and ECG findings are presented in Table I

Twenty patients with clinical LBBB served as a control group Their ages ranged between 31 and 84 years

Echocardiography was performed in the supine position with an Ekoline 20A echograph S K I utilizing a 0 5 inch diameter 2 25 mhz transducer focused at 10 cm with a repetition of 1 000

Table I Clinical and ECG findings in 22 patients with artificial pacemakers

Clinical diagnosis	*ECG findings before pacemaker*	*No of cases*
Adams Stokes syndrome	Complete A V block	9
Anterior wall myocardial infarction	Complete A V block left axis and right bundle branch block	[illegible]
Coronary insufficiency	*Second degree A V block* Mobitz type II	4
Scleroderma heart disease	Sinus rhythm with right bundle branch block and left posterior hemiblock	1
Atrial septal defect	Congenital complete A V block	1
Sick sinus syndrome	Marked sinus bradycardia with episodes of atrial flutter	[illegible]
Primary myocardial disease	Ventricular tachycardia	2
Calcific aortic valvular disease	Complete A V block	1
Total		22

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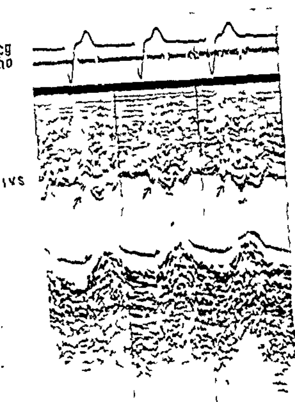


Fig 1 Simultaneous ECG PHO and ECHO of an 86-year old patient (case 1) with complete A V block and transvenous right ventricular pacemaker Paper speed 25 mm per second For detailed description see text

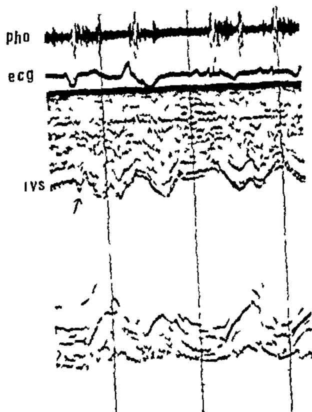


Fig 2 Simultaneous ECG PHO and ECHO of a 60-year-old patient (case ?) with recurrent ventricular tachycardia and temporary transvenous right ventricular pacemaker in fixed mode Paper speed 25 mm per second

impulses per second The ultrasound transducer was placed in the fourth or fifth left intercostal space close to the sternum The signal from the echograph was displayed and recorded on an Electronics for Medicine VR6 strip chart multi channel oscilloscopic recorder Ultrasonic scans were obtained from apex to base and echocardio grams were recorded with rigid adherence to the technique and criteria previously established' and routinely used in this laboratory The interven tricular septum was recorded at the level of both mitral leaflets and toward the left ventricular apex

Vectorcardiograms were recorded in frontal horizontal and right sagittal planes with Hart Electronics P V 5 vectorcardiograph The VCG loops were interrupted at the rate of 500 times per second by the large end of the time dash

The techniques and criteria for VCG parameter analysis were those previously reported from this laboratory Bipolar pacemakers were used in 12 cases and unipolar pacemakers were used in 10 cases

Results

ECHO findings

Pattern A Sixteen patients were found to have ECHO findings of abnormal septal motion (see Table II) The abnormality demonstrated in this group of patients with apical right ventricular endocardial pacemakers is an initial brief very active posterior movement of the left side of the interventricular septum occurring within 70 msec (range 40 to 100 msec) of the pacemaker artifact This motion lasted for 40 to 50 msec and then the septum moved posteriorly continuing its normal movement throughout ventricular systole

This pattern is well illustrated in Fig 1 (indi cated by an arrow) Fig 2 clearly illustrates that during sinus conducted beat (third beat) and during premature ventricular beat (second beat), septal motion fails to show the abnormal initial movement seen in pacemaker induced beat (first beat)

Pattern B (see Table II) In four patients with inserted pacemakers following the initial brief posterior septal movement, there was flat or

Table II ECHO and VCG correlations

Diagnosis	*No of cases*	*ECHO*		*VCG orientation of initial vector*	*Maximum VCG*
		Initial septal motion	*Septal motion during ejection period*		
Pattern A					
Adams Stokes syndrome	8				
Coronary insufficiency	4				
Primary myocardial disease	2				
		Brief posterior	Posterior	Superiorly posteriorly and to left	Superiorly posteriorly and to left
Sick sinus syndrome	1				
Scleroderma heart disease	1				
Total	16				
Pattern B					
Anterior myocardial inf	2		Anterior	Superiorly posteriorly and to right	Superiorly posteriorly and slightly to right
Atrial septal defect with epicardial right ventricular pacemaker	1	Brief posterior in 4 cases	Flat	Superiorly posteriorly and to left	Superiorly posteriorly and to left
Adams Stokes syndrome	1		Anterior		
Total	4				
Pattern C					
Sick sinus syndrome with malplacement of pacing electrode	1	Flat	Posterior	Inferiorly posteriorly to left	Superiorly posteriorly to left
Calcific aortic valvular disease	1	Flat	Posterior	Superiorly posteriorly and to left	Superiorly posteriorly and to left
Total	2				

anterior motion of the septum during the ejection period Two of these patients had anterior wall myocardial infarction (Fig 3) and a third had atrial septal defect and right ventricular apical epicardial pacemaker (Fig 4)

Pattern C (see Table II) In two patients an initial brief posterior septal motion was not recorded before the septum moved posteriorly One of them had malplacement of the pacing electrode and the other had calcific aortic valve disease

In the control group, 18 of 20 patients with clinical LBBB showed a dynamic posterior motion of the septum occurring within 40 msec of the onset of QRS preceding the anterior or flat motion away from the posterior left ventricular wall during ejection period

VCG findings In 16 patients with artificial pacemakers and Pattern A ECHO the initial QRS vector was oriented superiorly posteriorly and to the left (Table II) The maximum QRS vector was inscribed in the left superior and posterior octant very close to the sagittal plane (Fig 5) This VCG pattern is invariably observed in all patients with artificial pacemakers inserted in the endocardial apical area of the right ventricle[7, 9]

In four patients with Pattern B ECHO the QRS vector differed from this pattern (Table II) In two patients with extensive anterior wall myocardial infarction the initial QRS vector was displaced to the right Both the centrifugal and the centripetal limbs were pushed to the right (Fig 6) In the other two cases with Pattern B ECHO the spatial QRS loop resembled that recorded in Pattern A ECHO

Malplacement of the electrode high in the right ventricle resulted in one case in an initial inferior orientation of the QRS loop in the frontal plane (Pattern C ECHO Table II)

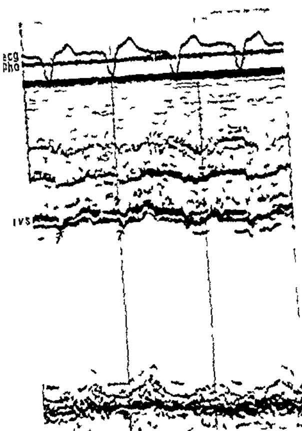


Fig 3 Simultaneous ECG PHO and ECHO of a 67 year old patient (case 3) with anteroseptal myocardial infarction and temporary transvenous right ventricular pacemaker Paper speed 25 mm per second.

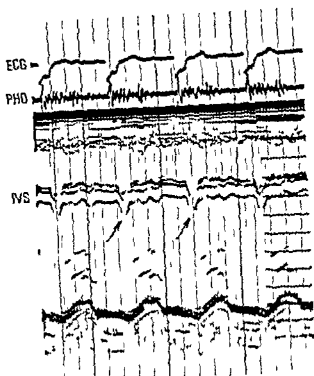


Fig 4 Simultaneous ECG PHO and ECHO of a 22 year old patient (case 4) with atrial septal defect congenital complete A V block, and epicardial right ventricular pacemaker Paper speed 25 mm per second

In the control group with clinical LBBB the initial QRS vector was oriented anteriorly inferiorly and to the left (Fig 7)

Discussion

The pattern of motion exhibited by the echoes from the interventricular septum in our patients with artificially induced LBBB is different from the echocardiographic septal findings of clinical LBBB The initial brief dynamic posterior motion occurring within 70 msec (range 40 to 100 msec) of the pacemaker artifact and lasting 40 to 50 msec was recorded in 16 cases (Pattern A) with transvenous endocardial right ventricular pacing But in difference from natural LBBB this rapid short dynamic posterior movement was not followed in systole by an anterior (paradoxical) or flat motion During the ejection period the septal motion was normal The initial abnormal septal motion exhibited in patients with right ventricular apical pacing requires a normal septum and an accurate positioning of the tip of the catheter Malplacement of the tip of the catheter high in the right ventricle resulted in a flat initial septal motion in one patient (Pattern C Table II)

There is also a noticeable time difference in the initial abrupt posterior motion between the two groups (it is within 40 msec after QRS onset in the clinical LBBB group vs 70 msec in the pacemaker group) This time difference between groups may also possibly be related to the difference in the orientation of the initial forces of QRS loop vector to the left and superiorly in artificial pacemakers and to the left anteriorly and inferiorly in most patients with clinical LBBB

In two patients with anterior myocardial infarction there was rather anterior (paradoxical) movement of the septum (Pattern B) during the ejection period instead of the posterior movement following the initial brief posterior motion as described in Pattern A

Moreover epicardial implantation of the pacemaker electrode in the right ventricular apex near the interventricular septum resulted in an

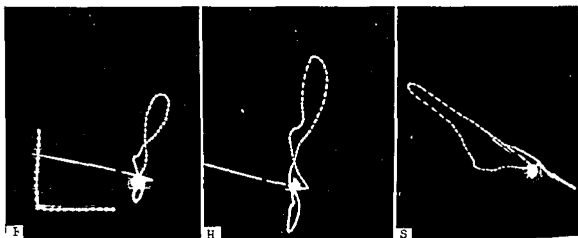


Fig 5 Pacemaker vectorcardiogram case 1 Time-dash 2 msec

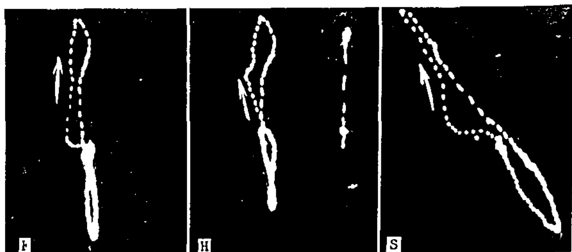


Fig 6 Pacemaker vectorcardiogram case 3 Time dash 2 5 msec

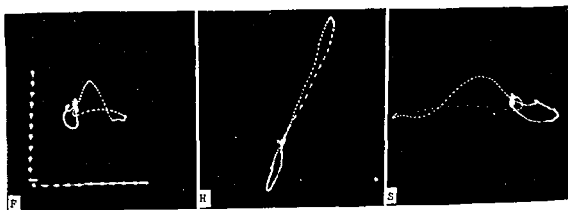


Fig 7 Vectorcardiogram of a patient from the control group with natural LBBB

initial posterior septal motion as seen in Pattern A followed by flat motion throughout systole Thus in a single patient with epicardial pacing (Fig 4) the initial posterior movement is present Further studies of similar cases may add more specific data concerning septal motion in right ventricular epicardial pacing

Mechanism of abnormal septal motion The mechanism of abnormal septal motion in natural LBBB and in pacemaker induced LBBB remains uncertain However, the VCG data obtained by us correlated with those obtained by echocardiography may offer a better explanation of this intriguing mechanical phenomenon

McDonald felt that in natural LBBB there is early activation and contraction of the septum but delay in activation and contraction of the left ventricular free wall due to a block in LBB or its branches thus explaining both phases in the abnormal septal motion the initial abrupt posterior movement of the septum followed by the paradoxical pattern Bevans and Rapaport[10]

claimed that the pre ejection posterior motion of the septum is due to the displacement from rising right ventricular isovolumic pressure that exceeds the pressure developed by the delayed left ventricular contraction

In natural LBBB and in the pacemaker induced LBBB the initial 20 to 30 msec vector is oriented from the right to the left instead of from left to right as recorded in normal individuals However whereas in clinical LBBB the initial vector is oriented to the left anteriorly and inferiorly in artificial LBBB it is directed to the left posteriorly and superiorly The difference between the maximum QRS vector in both situations is also seen in the frontal plane in clinical LBBB the maximum QRS vector is oriented mostly inferiorly occasionally superiorly where as in artificial LBBB the frontal plane vector is always oriented superiorly [7, 8] Hence there is a certain type of septal depolarization in clinical LBBB which cannot be duplicated by stimulating the right septal surface [9] Whereas natural LBBB by itself is an infrequent cause of abnormal QRS left axis deviation artificially induced LBBB is a constant cause of abnormal QRS left axis deviation Natural LBBB and pacemaker induced LBBB are similar but not identical Differences in activation may thus result in variations of septal motion

It is therefore tempting to assume that the superior and posterior orientation of the artificially induced QRS loop as proved by vectorcardiography causes early depolarization of the left ventricle while the depolarization of the septum is still in progress The left ventricular wall motion not being excessively delayed the septum is not yet relaxed Hence paradoxical anterior motion of the septum induced by the delayed left ventricular contraction which occurs in natural LBBB does not take place in artificially induced LBBB

In natural LBBB the activation of the left ventricle seems to take various pathways as proposed by at least four theories [1-5] whereas in patients with artificial pacemaker the fast spread of activation starts from one single well defined area the apex of the right ventricle

In anterior and anteroseptal myocardial infarction and inserted pacemaker displacement and delay of the initial and maximal QRS vectors cause abnormalities in the entire activation system and hence in the pattern of the vectorcardiogram [11] These changes in the sequence of activation in turn may cause delayed contraction of the left ventricular free wall which pulls anteriorly the interventricular septum

Additional septal motion abnormalities such as flat or anterior paradoxical motion of the septum raised our index of suspicion of the presence of other associated cardiac abnormalities such as anterior myocardial infarction right ventricular overload etc Such patterns when recorded could have diagnostic implications

Summary

Twenty one patients with transvenous endocardial right ventricular pacemakers and one patient with epicardial right ventricular pacemaker inducing artificial left bundle branch block (LBBB) were studied with echocardiographic and vectorcardiographic techniques

Sixteen patients were found to have an initial very active posterior motion of the interventricular septum occurring within 70 msec (range 40 to 100 msec) of the pacemaker artefact followed by posterior movement during the ejection period (Pattern A) Eighteen of 20 patients with clinical LBBB serving as a control group showed a dynamic posterior motion occurring within 40 msec of the onset of QRS and preceding anterior (paradoxical) motion of the septum during ejection

In four patients following the initial brief posterior septal movement there was flat or anterior movement of the septum during the ejection period (Pattern B) Two patients had myocardial infarction and one had atrial septal defect and epicardial right ventricular pacemaker Only in two patients the initial brief posterior septal motion was not recorded before moving posteriorly during the ejection period (Pattern C)

The different patterns of septal motion found in patients with artificial LBBB and in those with natural LBBB could be explained by differences in activation of the heart as shown by vectorcardiography

Echocardiographic septal evaluation of patients with artificial pacemakers could have diagnostic implications in suggesting possible underlying complicating cardiac abnormalities

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REFERENCES

1 *Popp R L Wolfe S B Hirata T et al Estimation of* right and left ventricular size by ultrasound A study of the echoes from the interventricular septum Am J Cardiol **24** 523 1969
2 McDonald I G Echocardiographic demonstration of abnormal motion of interventricular septum in left bundle branch block Circulation **48** 272 1973
3 Dillon J C Chang S *and Feigenbaum H Echocar* diographic manifestations of left bundle branch block Circulation **49** 876 1974
4 Abbasi A S Eber L M MacAlpin R N and Kattus A A Paradoxical motion of interventricular septum in left bundle branch block Circulation **49** 423 1974
5 Chaithiraphan S Goldberg E and O Reilly M Abnormal septal motion in left bundle branch block Chest (abst) **66** 319 1974
6 Zoneraich S Zoneraich O and Rhee J J Echocardio graphic findings in atrial flutter Circulation **52** 455 1975
7 Zoneraich O Zoneraich S and Douglas A The vectorcardiographic findings in patients with artificial pacemakers Chest **53** 436 1968
8 *Zoneraich O and Zoneraich S Vectorcardiography of* ventricular ectopic beats in patients with coronary artery disease *in* Zoneraich S editor Non invasive methods in cardiology Springfield Ill 1975 Charles C Thomas Publisher pp 284 295
9 Castellanos A Lemberg L Salhanick L and Berko vits B V Pacemaker vectorcardiography AM HEART J **75** 6 1968
10 Bevans L C and Rapaport E An echocardiographic study of left ventricular septal and posterior wall motion in left and right bundle branch block (abst) Clin Res **21** 234 1973
11 Rodriguez M I and Sodi Pallares D The mechanism of complete and incomplete bundle branch block Am HEART J **44** 715 1952
12 Becker R A Scher A M and Erickson R V Ventricular excitation in experimental left bundle branch block AM HEART J **55** 547 1958
13 Grant R P and Dodge H T Mechanisms of QRS complex prolongation in man Left ventricular conduction disturbances Am J Med **20** 834 1956
14 Barker J M The unipolar electrocardiogram A clinical interpretation New York 1952 Appleton Century Crofts Inc
15 *Bryant J M Interventricular conduction in* Rossmann C E editor Advances in electrocardiography New York 1958 Grune & Stratton Inc
16 Zoneraich O and Zoneraich S Pacemaker vectorcardiography in patients with myocardial infarction and intraventricular conduction defects *in* Hoffman I editor Vectorcardiography 2 Amsterdam 1971 North Holland Publishing Company p 317
17 Zoneraich S and Zoneraich O Newer vectorcardiographic findings in patients with myocardial infarction and artificial pacemakers *in* Hoffman I and Hamby R editors Vectorcardiography 3 Amsterdam 1976 North Holland Publishing Company pp 149 154

Precordial ST segment mapping 3 Stability of maps in the early phase of acute myocardial infarction

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With the effective prevention and management of primary cardiac arrhythmias in the early phase of acute myocardial infarction (MI) morbidity and mortality due to electrical derangements have been markedly curtailed in the Coronary Care Unit (CCU) Morbidity and mortality currently encountered in the CCU are related primarily to power failure of the ischemic *left ventricle This* syndrome presents as a spectrum ranging from mild (sometimes even subclinical) congestive heart failure to cardiogenic shock[2] The latter entity is associated with necrosis of a *critical mass* of myocardium estimated to be more than 35 to 40 per cent of the entire left ventricle[3] *Efforts to* further reduce complications and death have therefore been concentrated upon application of methods currently believed to reduce the amount of myocardial ischemic injury or to prevent extension

Modification of infarct size has been accomplished in experimental MI using various interventions by Maroko and associates[7] Such interventions have been monitored by methods which *estimate* the magnitude and extent of ischemic injury Methodology includes epicardial and precordial ST segment mapping

Significant experience with precordial ST mapping in following *patients with MI in the* CCU has already been accumulated Assessment *of interventions can be accomplished* by serially monitoring changes of ST segment elevation *recorded* from multiple sites over the anterior *thorax* *Although* the technique has been found reproducible and stable by some workers in both animals and patients the opinion has been voiced by other investigators that ST maps are unstable and non representative of changes of the injured area especially in the early phase of MI[4] Since *interventions are probably* most effective in the first few hours after inception of the coronary *attack* it is important to evaluate the natural course of precordial ST maps in this period This study reports our observations on the stability of ST maps in the early phase of acute MI

Material and methods

Thirty one consecutive *patients with the* presumptive diagnosis of acute anterior MI were studied The diagnosis was based on a history of chest pain of over one hour s duration and the presence of ST elevation in the precordial standard leads Particular emphasis in the history taking was placed on finding *the exact* time of onset of chest pain The *diagnosis of MI* was subsequently confirmed in 28 patients by enzyme curves pathognomonic of infarction and evolutionary ECG changes one patient had early repolarization with ST elevation later *shown to* be abolished during exercise and two *patients* had ventricular aneurysms with stable ST elevation for several months following previous myocardial infarction Of the group of 28 patients with MI 23 were male and 5 were female Their mean age was 56 7 ± 1 7 (S E M) with a range of

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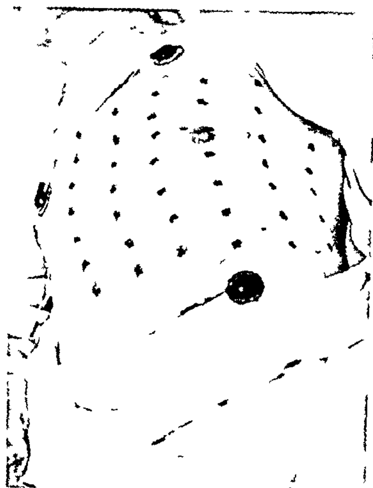


Fig 1 Location of the 49 marks which were made on the surface of the chest and from which recordings were made The seventh vertical column at the posterior axillary line is not depicted in this photograph

36 to 70 years Fourteen of the patients were in Killip Class I nine in Class II and five in Class III Patients in Killip Class IV (cardiogenic shock) were not included in the study [9] Clinical classification refers here to the initial clinical presentation of the patients Patients with bundle branch block or pacemaker triggered rhythm were also excluded The routine management of patients was not affected by the study and patients received drugs and other treatment as clinically indicated

Precordial ST segment maps were obtained by recording via the V lead of a Hewlett Packard 1511A ECG machine from 49 sites made on the chest of the patients by a skin pencil (Fig 1) Marking of the chest assured accurate repositioning of the V lead A Welsh self retaining electrode (HP part No 9301 0122) with a contact diameter of 15 mm was used in all studies The 49 marks made on the chest formed a grid of seven transverse rows each including seven recording points (Fig 1) The seven rows were designated A to G starting from above The seven points of each row were arranged from the right sternal border (point 1) to the posterior axillary line (point 7) The first mark (A_1) was made at the second intercostal space to the right of the sternum The A mark was made at the second intercostal space to the left of the sternum Mark A_5 was made at the anterior axillary line and A_3 and A_4 were placed equidistant between A_2 and A_5 A_6 and A_7 points were put on the mid and posterior axillary lines Rows B to G followed as above Distance between rows was identical to that between the second to third intercostal space (Fig 1) Distance between transverse rows or vertical columns depended on the size of the chest of individual patients The initial precordial map (a), which required 12 to 15 minutes to perform was followed by measurement of blood pressure using a cuff sphygmomanometer Following this initial assessment one of the authors remained at the bedside for the purpose of continually assessing the clinical status of the patients Approximately one hour later second precordial map (b) was made followed by measurement of blood pressure The initial map of the 28 patients was performed 6 1 ± 0 8 (range 1 0 to 21 5 hours after the onset of chest pain and time between maps a and b in these patients was 61 0 ± 3 4 (range 35 to 109) minutes

The sum of ST elevations at all sites in mm (ΣST) was taken as an index of ischemic damage and the number of points which showed 1 0 mm or more ST elevation (NST) was taken as an expression of the extent of ischemic injury [7, 10] ST elevation was measured to the nearest 0 5 mm 0 06 sec from the nadir of the S wave using the T P segment as isoelectric line In the absence of S waves measurements were done 0 06 sec after the peak of the R wave In the presence of tachycardia with a poorly identified TP segment the PR interval was used as a baseline [10] Heart rate measurements were based on averaging 15 to 20 R R intervals of the last lead of precordial ST maps The paired t test was used in analyzing data of the two sets of measurements The results are reported as mean ± SEM

Results

The time of the initial study in relation to the onset of chest pain the time between maps a and b data from precordial ST mapping and blood pressure and heart rate measurements along with

Table I Clinical and precordial mapping data of patients with anterior myocardial infarction

Pt	Age of MI (hours)	a to b Time interval (min)	Σ ST (mm)		NST		Systolic BP (mm Hg)		Diastolic BP (mm Hg)		Heart Rate (beats/min)		Clinical status during the study
			a	b	a	b	a	b	a	b	a	b	
1	6 0	78	47 0	47 0	24	23	168	164	113	110	93	98	Stable chest pain
2	2 0	68	49 0	73 5	25	30	134	134	83	81	98	103	Exacerbation of chest pain between a and b
3	10 0	65	15_5	15? 0	40	38	13?	132	92	92	90	9?	Stable chest pain
4	9 0	64	9? 0	89 0	?5	?6	180	182	118	123	96	97	Stable slight chest discomfort
5	1? 0	68	92.5	91 5	3?	3?	108	106	7_	80	9?	93	Stable chest pain
6	1 3	5_	80 0	78 5	19	19	134	1?2	9?	95	98	9_	Stable chest pain
?	3 0	58	30 5	29 5	14	14	150	134	110	102	84	83	Stable right arm pain
8	10 0	6?	1?1 5	1?0 0	39	40	138	14?	90	84	106	100	Stable chest pain
9	5 0	40	49 0	48 5	21	19	158	154	104	106	8	7_	No chest pain
10	21 5	60	?5	2_5	18	1	150	148	100	96	84	86	No chest pain
11	5 0	68	1?8 5	1?3 0	37	3_	150	15?	105	105	113	110	No chest pain
1?	5 0	3	8_5	89 0	?8	?9	116	110	90	8_	8_	82	No chest pain
13	12 0	4_	164 5	168 0	39	39	164	163	100	99	86	86	Stable slight chest ache
14	5 0	36	110 0	107 5	31	30	1?8	123	90	88	117	12?	Stable severe chest pain
15	1 5	8	39 5	? 0	23	14	118	1?8	8_	90	?8	83	No chest pain
16	5 0	39	49 0	4? 5	?	21	1_?	149	98	101	98	100	Stable chest ache
17	5 0	49	10 5	10 5	3	3	107	108	?6	77	73	?0	Stable slight chest ache
18	16 0	4?	17 0	1 0	11	8	1?0	123	80	5	63	64	Stable slight chest ache
19	1 0	60	24 5	24 5	14	16	140	14?	90	88	?0	?2	Stable chest pain
?0	5 7	58	?1 0	6 0	11	1	1?4	1?6	?8	6	72	?7	No chest pain pulmonary edema during a
?1	5 0	?7	53 5	48 5	24	2?	108	110	?8	?8	79	?8	Stable slight chest ache left arm pain
??	1 ?	53	4 0	29 5	??	16	165	164	115	108	8	74	Transient severe chest pain during a slight pain during b
23	5 0	109	39 5	4? 5	?4	2?	115	114	6	?4	?5	6	Stable back pain
?4	3 5	55	139 0	13_5	3?	37	115	118	80	8_	88	93	Stable severe chest pain
2?	3	104	23 0	1 0	13	8	100	105	8?	82	?6	?4	Recurrent episodes of ventricular fibrillation
??	4 5	5	31 5	31 5	?	19	1 4	1?6	88	88	60	84	Stable chest tightness
?	4 0	60	30 5	?8 5	1	16	90	9_	68	0	104	10_	Stable slight chest ache
?8	1 0	80	91 5	9? 5	35	32	110	110	90	?0	94	94	No chest pain
Mean	6.1	61 0	65 8	63 8	23 9	2? 3	13 0	131 ?	91 2	90 3	87 4	88 1	
±S.E.M	0 8	3.4	8 4	8 ?	4	4 2	4 3	4 1	2.4	2 4	? 4	_5	
P value			P > 0 1		P < 0 0?		P > 0 8		P > 0.2		P > 0 2		

Abbreviations. BP blood pressure other abbreviations as in the text

details on the clinical status of the patients during the study are shown in Table I

In the 28 patients with anterior myocardial infarction there was no significant change in mean values for ΣST between maps a and b and blood pressure and heart rate measurements remained stable (p > 0 05) A small but statistically significant decline of NST occurred (p < 0 02) In 23 patients changes of ΣST varied in the relatively narrow range from −5 5 to +3 5 mm and changes in NST varied from −3 to +2 In the remaining five patients greater changes occurred In patient No 15 a drop in ΣST of 12 5 mm and a decline of NST of 9 occurred without an apparent change in the clinical status (Table I Fig 2) In the other four patients clinical status varied considerably during the two precordial maps patient No 2 suffered a severe exacerbation of chest pain between maps a and b and this was reflected by increase in ST elevation in precordial map b (Table I Fig 3) Patient No 22 experienced a transient self limited episode of chest pain during performance of map a and ST segments declined by the time map b was

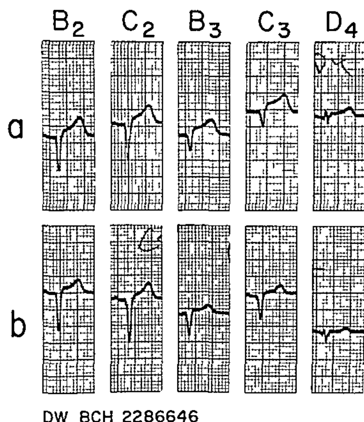


Fig 2 Selected tracings from the precordial maps (*a* and *b*) obtained 87 minutes apart in a 63 year old woman (Patient No 15) with an anteroseptal myocardial infarction Significant decline of ST elevation occurred between the two tracings without apparent explanation Capital letters denote transverse rows and numbers vertical columns

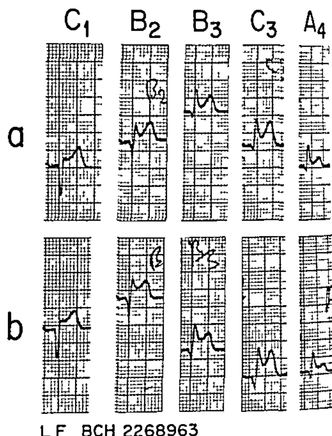


Fig 3 Selected tracings from the precordial maps (*a* and *b*) obtained 68 minutes apart in a 47 year old man (Patient No 2) with an extensive anterior myocardial infarction Marked increase of ST elevation occurred between the two tracings Severe pain occurred in the interim Capital letters denote transverse rows and numbers vertical columns

performed (Table I Fig 4) Patient No 25 had map a recorded shortly after several episodes of ventricular fibrillation and patient No 20 had the initial study performed while an episode of pulmonary edema was resolving in both instances substantial reduction in ST elevations were noted in the second map (Table I Figs 5 and 6) Changes in ΣST elevation varied in these four patients from −18 to +24 5 mm and NST from −10 to +5

Separate analysis of the subgroup of 24 clinically stable patients (Table I) revealed a ΣST of 70 9 ± 9 4 at a and 69 5 ± 9 4 at b ($p > 0\,05$) There was still a small but statistically significant decline of the NST from 25 0 ± 2 0 at a to 23 7 ± 2 0 at b ($p < 0\,02$) On regression analysis there was no correlation of the timing of the first study in relation to the inception of the chest pain or time interval between a and b with the changes of ΣST or NST This was found in both the analyses of all the 28 patients and the subgroup of the 24 clinically stable patients

Discussion

Stability of the precordial ST segment maps is a prerequisite for their application in the evaluation of therapeutic interventions directed at decreasing the magnitude of ischemic injury and resultant necrosis Of practical interest is the *study of the course of precordial maps* in the initial few hours following the inception of a coronary attack since in this time period interventions may be most effective [1]

To compare data from serial maps recordings should be made from fixed locations on the thorax Variations of up to 1 5 mm in ST elevation have been produced by changing the location of the recording electrode by only one cm in one series of patients [10] In addition *measurements* of the degree of ST elevation should be carried out following rigidly defined criteria [1]

Studies of the natural course of ΣST in patients with uncomplicated anterior MI have shown a decline of 29 per cent[7] and 32 per cent[10] in the first 24 hours following the initial study Gold and

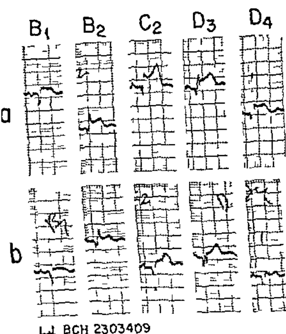


Fig 4 Selected tracings from the precordial maps (a and b) obtained 53 minutes apart in a 61 year old man (Patient No 22) with an anterior myocardial infarction Marked reduction of ST elevation occurred between the two tracings A severe self limited chest pain episode occurred during the first recording Capital letters denote transverse rows and numbers vertical columns.

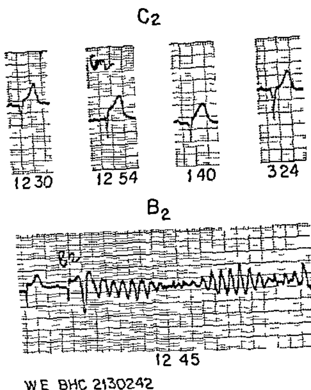


Fig 5 The upper panel shows selected tracings from the precordial maps obtained in a 47 year old man (Patient No 25) with an anteroseptal myocardial infarction Significant increase of ST elevation occurred between 12 30 and 12 54 Ventricular fibrillation occurred in the interim Other episodes of ventricular fibrillation followed Precordial maps obtained 104 minutes apart at 1 40 and 3 24 showed decline of ST elevation with time Capital letters denote transverse rows and numbers vertical columns

associates have found the precordial maps to be stable in six patients studied within six hours of inception of MI during a one hour control period before administration of propranolol Maroko and colleagues in 11 patients with MI have found a decline of ΣST to 93 5 per cent and NST to 98 per cent two hours following the initial study patients were examined within eight hours of onset of chest pain but the group included subjects with extension of MI as expressed by the small decline of ΣST and NST 24 hours following the initial study Flaherty and co workers have found ΣST to be stable in five patients studied with a 16-lead ECG system at 60 90 and 120 minutes after an initial precordial map Although stability of ΣST in these small groups of patients was demonstrated individual variations and their correlation with clinical status were not examined In contrast to these reports Reese and associates noted marked variation in precordial maps obtained over periods of time ranging up to 12 hours apart in four patients without change in clinical status or application of therapeutic interventions.

Parameters known to affect the magnitude of ischemic injury should be monitored if meaningful comparison of serial precordial maps is expected Hypotension and increase of the heart rate have been shown to increase ischemic injury as assessed from myocardial electrograms in conscious dogs with acute coronary occlusion [1] and preliminary studies indicate that hemodynamic changes may also influence precordial ST segments in patients with MI [3]

In our study precordial maps obtained approximately one hour apart revealed stable ΣST for the group as a whole Blood pressure and heart rate values also remained stable The small but significant reduction of NST may point to a slow gradual decrease of the extent of ischemic injury although the magnitude of damage as expressed by the ΣST did not change significantly This decline of NST did not correlate with the time of

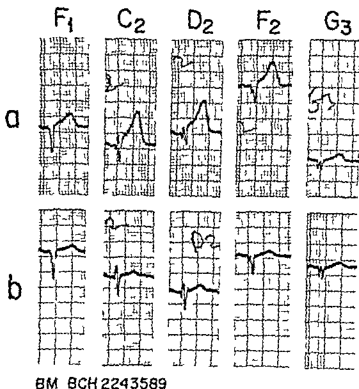


Fig 6 Selected tracings from the precordial maps (*a* and *b*) obtained 58 minutes apart in a 69 year old man (Patient No 20) with an anteroseptal myocardial infarction *Tracing a* was obtained while the patient was in pulmonary edema and *tracing b* showing marked resolution of ST elevation was made during a relatively asymptomatic period Capital letters denote transverse rows and numbers vertical columns

the initial study in relation to onset of pain or the time interval separating the two maps (Table I) It is probably a corollary of the above that practolol proved to be equally effective in decreasing NST in patients with MI admitted shortly after and up to 72 hours after onset of chest pain [5]

In four of the five patients showing marked changes in the map parallel changes in the clinical status were observed Exacerbation of chest pain resulted in increase of ΣST and NST and transient self limited chest pain led to transient alterations in the map One patient showed ST elevation after resuscitation from ventricular fibrillation, although the subsequent map showed a marked decline of ST elevation Chest pain and ventricular fibrillation have been observed by Maroko and colleagues to have a marked effect on the injury current recorded by the precordial map The decline of ST elevation following treatment of pulmonary edema in one patient might have been due to acute reductions in heart size and in left ventricular wall tension with resultant decrease of myocardial O_2 consumption [1] despite absence of changes in blood pressure or heart rate in this patient

It is possible that ischemic injury in the early phase of MI is modulated by several parameters Some of them like blood pressure and heart rate can be serially monitored Others, like the clinical status of the patient can also be observed readily but are qualitative in nature The effect on the injured heart of other factors such as neurohumoral status are less well defined [14] It is interesting that in patient No 15 blood pressure, heart rate and clinical status remained unchanged while a significant decline of ΣST and NST was recorded Levels of catecholamines in the plasma and urine have been found to be markedly elevated in patients during the early phase of acute MI [15,17] Also peaks of catecholamine release have been observed at times of psychological stress or during pain [16,1] Such factors might also play a role in altering ST segments in the absence of obvious changes in hemodynamics or clinical status

In conclusion, closely spaced precordial ST segment maps are stable for several hours following the inception of MI Variation of serial precordial maps may usually be explained on the basis of alterations in the clinical status which along with heart rate and blood pressure, should be closely monitored when precordial maps are used in the evaluation of interventions in the CCU However, changes of ST segment maps may occur without an apparent clinical reason and this points to the necessity of including large enough numbers of patients in intervention studies to allow for such variation

Summary

To evaluate the stability of precordial ST segment mapping techniques in assessing ischemic myocardial injury we studied 28 patients with acute anterior myocardial infarction using a 49 lead electrocardiographic system (1 mV = 10 mm) The sum of ST elevations in millimeters was taken as an index of ischemic injury and remained stable in two consecutive maps made approximately one hour apart (65 8 ± 8 4 vs 63 8 ± 8 7 mm) The number of sites showing ST elevation ≥ one mm was taken as an index of extent of injury and showed a small but statistically significant decline (23 9 ± 4 5 vs 22 3 ± 4 2 mm) during the same time interval Blood pressure and heart rate

—mained stable Changes in the map were observed in five patients but could be explained in four by abrupt alterations in clinical status In one patient no explanation for alterations in the map was apparent We conclude that precordial ST segment maps are usually stable in the early stages of anterior myocardial infarction but should be used to evaluate interventions only with careful clinical monitoring and with the knowledge that occasional unexplained variations do occur

REFERENCES

1 Braunwald E and Maroko P R The reduction of infarct size—an idea whose time (for testing) has come Circulation 50 206 1974
2 Ross, J Jr Hemodynamic changes in acute myocardial infarction, chap 23 in myocardium Failure and infarction, Braunwald E (ed) New York 1974 Hospital Practice Publishing Co Inc p 261
3 Page D L Caulfield J B Kastor J A DeSanctis R W and Sanders C A Myocardial changes associated with cardiogenic shock N Engl J Med 285 133 1971
4 Maroko P R Davidson D M Libby P Hagan A D and Braunwald E Effects of hyaluronidase administration on myocardial ischemic injury in acute infarction Ann Intern Med 82 516 1975
5 Pelides, L J Reid D S Thomas M and Shillingford J I Inhibition by β blockade of the ST segment elevation after acute myocardial infarction in man Cardiovasc Res 6 295 1972
6 Flaherty J T Reid P R Kelly D T Taylor D R Weisfeldt M L and Pitt B Intravenous nitroglycerin in acute myocardial infarction Circulation 51 132 1975
7 Maroko P R Libby P Covell J W Sobel B E Ross J Jr and Braunwald E Precordial ST segment mapping An atraumatic method for assessing alterations in the extent of myocardial ischemic injury The effects of pharmacologic and hemodynamic interventions Am J Cardiol 29 223 1972
8 Reese L Scheidt S and Killip T Variability of precordial ST segment maps after acute myocardial infarction in man (Abstr) Circulation 48 (Suppl IV) IV 38 1973
9 Wolk M J Scheidt S and Killip T Heart failure complicating acute myocardial infarction Circulation 45 1125 1972
10 Madias, J E Venkataraman K and Hood W B Jr Precordial ST-segment mapping 1 Clinical studies in the Coronary Care Unit Circulation 52 799 1975
11 Gold H K Leinbach, R C and Maroko P R Reduction of myocardial injury in patients with acute infarction by propranolol (Abstr) Circulation 50(Suppl III) III 33 1974
12 Redwood P R Smith E R and Epstein S E Coronary artery occlusion in the conscious dog Effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia Circulation 46 323 1972
13 Shell W E, and Sobel, B E Protection of jeopardized ischemic myocardium by reduction of ventricular after load N Engl J Med 291 481 1974
14 Radvany P, Maroko P R and Braunwald E Effects of hypoxemia on the extent of myocardial necrosis after experimental coronary occlusion Am J Cardiol 35 795 1975
15 Gazes P C, Richardson, J A and Woods E F Plasma catecholamine concentrations in myocardial infarction and angina pectoris Circulation 19 657 1959
16 Valori, C, Thomas M and Shillingford J Free noradrenaline and adrenaline excretion in relation to clinical syndromes following myocardial infarction Am J Cardiol 20 605 1967
17 Klein R F Troyer W G Thompson H K Bogdonoff M D and Wallace A G Catecholamine excretion in myocardial infarction Arch Intern Med 122 476 1968

Sodium nitroprusside as a coronary vasodilator in man

I. Effect of intracoronary sodium nitroprusside on coronary arteries, angina pectoris, and coronary blood flow

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Although sodium nitroprusside has long been known to be a potent, rapid-acting peripheral vascular smooth muscle relaxant, it became available commercially only recently. Its effect is almost immediate and ends within minutes. The brief duration of action is said to be due to its rapid conversion to thiocyanate,[1] which is far less active as a vasodilator. Intravenous infusion of the agent has been used successfully in hypertensive crises[3,4] as well as in patients with acute myocardial infarction, refractory congestive heart failure, and/or cardiogenic shock, where improvement in left ventricular function is obtained by reduction of preload and afterload by relaxing the smooth muscle of peripheral arteries and veins without significantly altering heart rate.[8] Intra-arterial and intravenous[1] infusions of the compound have produced direct vasodilation in patients with arterial insufficiency, e.g., cases of ergot poisoning. However, despite the abundant evidence showing nitroprusside's effect on the peripheral circulation, little information is available concerning its direct action on coronary arteries and what is available is somewhat contradictory.[9-11] Therefore, the present study was initiated to determine the effect of the drug on (1) the arteriographic appearance of the coronary arteries in patients undergoing diagnostic coronary arteriography and on angina pectoris developed (spontaneously) during the cardiac catheterization and (2) coronary blood flow rate in patients undergoing coronary artery bypass surgery.

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Methods

A total of 21 patients were studied during cardiac catheterization. Sixteen of these individuals were male and five were female, with an average age of 53 ± 2 years (mean ± S.E.). Any patient suspected of having muscular bridges were excluded from this study. Our study participants were subdivided into three groups according to the dose of sodium nitroprusside used and the condition of the coronary arteries (Table I).

The subjects were studied during the postabsorptive state while under sedation with sodium pentobarbital and meperidine hydrochloride. Arterial blood pressure and electrocardiographic (ECG) monitoring took place continuously. The left ventricular angiogram was taken in both the right anterior oblique (RAO) 20° and then the left anterior oblique (LAO) 60° position with Renog

afin 76 (66 per cent meglumine diatrizoate and 0 per cent sodium diatrizoate) Selective coronary arteriography was then performed with the technique of Sones and Shirey in both the RAO and LAO views For the purpose of our study the right or left coronary arteriogram was obtained in the same angle under control conditions and immediately after intracoronary injection of 0 5 to 1 ml of 5 per cent dextrose in water (D,W Group I) or 5 or 10 μg of sodium nitroprusside dissolved in the same volume of D,W (Groups II and III) Injections of small amounts of Renografin 76 were used to delineate coronary anatomy so as to ensure the proper delivery of the solutions into the coronary artery being studied The interval between the arteriograms was approximately 5 minutes the arterial blood pressure and heart rate changes induced by coronary arteriography had returned to the control level within 2 minutes after the radiopaque dye injection

Four patients in Groups II and III who developed angina pectoris during catheterization were treated with 5 to 10 μg of sodium nitroprusside injected into the left main coronary artery

In addition two patients were studied intraoperatively approximately 30 minutes after the patients were taken off the cardiopulmonary bypass In both instances sodium nitroprusside (5 μg) was injected into a saphenous vein graft bypassing a severe proximal right coronary artery occlusion Graft blood flow was measured with a Micron electromagnetic flowmeter (MU 1001 B) connected to a flowprobe of appropriate size Arterial blood pressure and the ECG were also monitored continuously throughout the period of study and the blood thiocyanate level was determined several minutes after the administration of sodium nitroprusside

Informed consent was obtained from each patient who participated in our studies

Preparation of the stock and working solutions of sodium nitroprusside A 2 5 ml amount of D W (Travenol Laboratories) was used to dissolve 50 mg of sodium nitroprusside in powder form (Nipride Roche Laboratories) The final concentration of the fresh stock sodium nitroprusside solution was 20 mg per milliliter The working solution of the compound with a final concentration of 10 μg per milliliter was made up by diluting the stock solution with D W The solutions were protected from light by wrapping their containers in aluminum foil Those contain-

Table I Groups of study participants

Group	No	*Age (yr)*	*Sex (M/F)*	*Dosage of sodium nitroprusside (μg)*	*Condition of coronary arteries*
I	5	44 ± 2	3/2	0	Normal
II	11	54 ± 2	8/3	5	Multiple vessel lesions
III	5	61 ± 2	5/0	10	Multiple vessel lesions

ing nitroprusside were not kept longer than 2 hours

Equipment The angiography equipment comprised a Phillips 3 phase 6 image intensifier system a 35 mm camera and a Cordis rotary cradle A Medrad injector set at 3 ml per second and at a pressure not exceeding 300 psi at the injector outlet for 3 seconds was used for the injection of Renografin 76

Data analysis Measurements of the caliber of coronary arteries with and without proximal stenotic lesions were carried out by two independent cardiologists with a 1 mm grid scale photographed on 35 mm film as a calibration reference The mean values of the two readings were used for statistical comparison When proximal stenotic lesions were present the caliber of the vessel at the lesion and that of the normal segment immediately proximal were measured Changes in heart rate blood pressure and coronary artery caliber induced by injections of Renografin 76 with and without preceding sodium nitroprusside were measured The paired t test was used for statistical analysis

Results

Responses of normal and stenosed coronary arteries to nitroprusside

Patients with normal coronary arteries In the control study (Group I) the diameter of the proximal segments of the same 20 coronary arteries in five patients were measured from two successive arteriograms obtained 5 minutes apart the second injection was immediately preceded by an intracoronary injection of 0 5 to 1 0 ml of D W The caliber of the coronary arteries remained essentially constant in the two sets of arteriograms—2 44 ± 0 1 mm vs 2 46 ± 0 11 mm $p > 0.71$



Fig 1A Effect of an intracoronary injection of 10 μg of sodium nitroprusside on the left coronary artery system in a 62 year old man with multiple coronary occlusive lesions The coronary arteriograms in *A* and *B* were photographed in the same RAO view with the same injector setting under control conditions (A) and immediately after the intracoronary injection of 10 μg of sodium nitroprusside (B) Note the vasodilation of the left coronary artery system induced by the drug especially at the proximal occlusive lesions of the left anterior descending coronary artery and the first obtuse marginal branch Radicals not noted before the use of the drug are readily visualized after sodium nitroprusside

Patients with occlusive coronary artery disease A total of 19 right and left coronary arteriograms were obtained from exactly the same angle in 11 patients in Group II before and immediately after the intracoronary injection of 5 μg of sodium nitroprusside Ten coronary arteriograms were similarly obtained from five patients in Group III who received 10 μg of intracoronary sodium nitroprusside Responses of normal and stenosed segments to nitroprusside in these studies were as shown in Table II

As shown in Table III the transient changes in blood pressure and heart rate caused by the intracoronary injection of the radiopaque dye after nitroprusside were essentially the same as those which occurred during the control coronary arteriograms (n = 22)

Figs 1*A* and 1*B* show the effect of sodium nitroprusside on the coronary arteries of one patient in Group III

Responses of angina pectoris to sodium nitroprusside Angina pectoris occurred during the performance of coronary arteriography of four patients with occlusive lesions in the left anterior descending artery and was promptly relieved after the injection of sodium nitroprusside (5 to 10 μg) into the left main coronary artery Anginal pain recurred in one of these subjects in 2 to 3 minutes but the patient responded later to sublingual nitroglycerin therapy The relief of anginal pain by nitroprusside was associated with a clear improvement of ST segment depression in all four patients

Graft flow studies In two individuals intragraft injections of sodium nitroprusside (5 μg) into aorta-right coronary artery saphenous vein grafts



Fig 1B See legend of Fig 1A

caused increases of mean graft flow from 38 and 50 to 62 and 80 ml per minute respectively The increases in vein graft blood flow occurred without any significant change in mean arterial blood pressure and lasted 1 to 2 minutes No alterations in heart rate rhythm or conduction were noted The blood levels of thiocyanate in both patients were reported as zero

Fig 2 demonstrates the responses of graft blood flow and arterial blood pressure to sodium nitroprusside in one of the patients As a result of this study subsequent studies of the effect of nitroprusside on (1) blood flow in aorta-right coronary artery vein grafts (2) cardiac electrophysiologic properties with the use of His bundle recordings and surface ECG and (3) hemodynamics were carried out in additional patients intraoperatively Increases in coronary blood flow as shown in Fig 2 were consistently observed after the administration of sodium nitroprusside in all patients studied Larsen and associates reported the flow effect of sodium nitroprusside as compared to papaverine hydrochloride A manu

Table II Responses to nitroprusside

	Coronary artery caliber (mm)	
	Normal segment	*Stenosed segment*
Group II		
Control	2.28 ± 0.15	1.26 ± 0.15
After nitroprusside	2.66 ± 0.20	1.61 ± 0.15
p value	< 0.01	< 0.0001
Group III		
Control	1.61 ± 0.14	0.69 ± 0.09
After nitroprusside	2.35 ± 0.14	0.90 ± 0.09
p value	< 0.01	< 0.05

Table III Changes caused by dye injection

	Δ mean BP (mm Hg)	*Δ heart rate (beats/min)*
Control	−[illegible]5 ± 1.4	−10.0 ± 2.4
After nitroprusside	−10.5 ± [illegible]6	−9.6 ± 2.6
p value	> 0.26	> 0.89

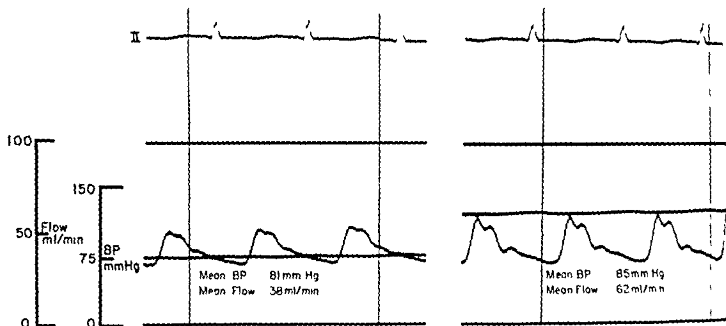


Fig 2 Effect of intragraft injection of 5 μg of sodium nitroprusside on ECG mean blood flow in an aorta right coronary artery saphenous vein bypass graft and arterial blood pressure The left panel shows control recordings The right panel was recorded 15 seconds after the injection of the drug during peak flow response Note that the coronary vasodilation induced by sodium nitroprusside occurred without any significant change in the heart rate the improved arterial blood pressure dp/dt_m from 570 (left panel) to 790 mm Hg per second (right panel) is consistent with improved left ventricular mechanical performance resulting from the nitroprusside induced improvement of myocardial perfusion

script reporting the electrophysiologic and hemodynamic effects of nitroprusside is being prepared

Discussion

Our coronary arteriographic data show that sodium nitroprusside increased the caliber of both normal and stenosed coronary arteries in man and that sodium nitroprusside per se at the dosages administered did not cause significant changes in heart rate or blood pressure Although the nitroprusside induced increase in coronary artery diameter occurred in the absence of any meaningful alteration in mean arterial blood pressure this finding alone could not be taken as evidence that sodium nitroprusside caused coronary vasodilation However studies performed in the operating room with direct monitoring of coronary blood flow and arterial blood pressure provide definite and unequivocal evidence that sodium nitroprusside is a potent vasodilator in human coronary arteries The promptness with which angina pectoris was relieved in our patients suggests that the agent improved the perfusion of the ischemic myocardium by directly relieving proximal obstruction of large coronary arteries where in man atherosclerotic lesions prevail The relief of angina pectoris by intracoronary nitroprusside in our patients would suggest that the coronary arteries in our subjects were not maximally dilated by hypoxia and that human coronary arteries could still respond to vasodilators even though the vessels may have been dilated by hypoxic metabolites This is particularly true when the limiting factor of coronary blood flow is the presence of obstructive lesion in the proximal segments of coronary arteries

The effect of the intravenous infusion of sodium nitroprusside on coronary hemodynamics has been previously studied in anesthetized dogs and in patients with acute myocardial infarction Rowe and Henderson[11] reported that intravenous infusion of the drug (8 μg per kilogram per minute) caused a 7 7 per cent decrease in mean arterial blood pressure a 29 7 per cent increase in cardiac output and a 52 6 per cent increase in coronary blood flow in dogs These investigators showed in effect a preferential coronary vasodilatory action on the part of sodium nitroprusside On the other hand, Chatterjee and his associates studying patients with acute myocardial infarction demonstrated that intravenous infusion of nitroprusside (16 to 200 μg per minute) caused a 24 to 29 per cent increase of the cardiac index and decreases of mean arterial blood pressure from 101 to 85 and from 83 to 74 mm Hg in Groups II and III of their patients respectively whereas coronary sinus flow measured by thermodilution

hniques tended to decrease in the absence of , significant changes in heart rate and left ntricular stroke work index either remained ichanged (Group II) or actually increased by a ean of 28 per cent (Group III) The former vestigation revealed that the mean left ventric ar oxygen usage increased 32 per cent during idium nitroprusside infusion The latter study owever showed a decrease in myocardial oxygen onsumption during nitroprusside infusion The i for the apparent disparity in observations f coronary blood flow during sodium nitroprus ide infusion is not clear at present Possible xplanations include differences in the rate of dministration of the drug the degree of the irug induced changes in and the subsequent modification of arterial blood pressure neart rate contractility coronary flow and coro nary venous drainage At any rate our flow studies established the finding that the direct orimary effect of sodium nitroprusside on human coronary arteries is vasodilatory

Organic nitrates the most common coronary vasodilators in clinical use have also been shown to increase the caliber of the coronary vascular bed Barner and associates reported that intra oronary injections of glyceryl trinitrate (nitro lycerin) caused a consistent increase in coronary flow in man Their finding is consistent with that reported by Eckstein and associates who administered nitroglycerin directly into canine coronary arteries and observed significant in creases in coronary blood flow in the absence of any meaningful change in the heart rate arterial blood pressure or myocardial oxygen require ment in three experiments Nitroglycerin admin istered sublingually—the regular route of admin istration of the drug—has on the other hand yielded a wide range of results on coronary blood flow Gorlin and associates found that nitrogly cerin given sublingually did not affect coronary vascular resistance in patients with essentially fixed coronary artery disease Coronary flow and oxygen consumption either were unchanged or actually decreased In normal subjects and in mild cases of cardiac disease Brachfeld and asso ciates reported coronary vasodilation occurring after sublingual nitroglycerin but attributed the vasodilation as secondary to an increase in myocardial oxygen requirements Fam and McGregor found that nitroglycerin adminis tered either intravenously or intra arterially caused a consistent decrease in resistance of large conductive coronary vessels Thus to us it appears that part of the difference in observation could be explained on the basis of a difference in the route of administration of the drug the nature and the degree of the occlusive lesion the functioning state of smooth muscle in the coro nary arterial wall the presence or absence and the function of collateral vessels the metabolic state of the myocardium as well as the extent to which reflex mechanisms modify the action of nitrates on the coronary circulation

Great interest has developed in sodium nitro prusside due to recent reports showing beneficial effects of the drug in patients with severely impaired left ventricular function This study provides additional new important information for a better and more complete understanding of the drug s action In addition to decreasing the preload and afterload the agent may cause bene ficial effects in patients with acute and chronic ischemic heart disease by improving myocardial perfusion and reducing the amount of tissue damage This improvement in coronary flow may apparently occur by relief of a muscular compo nent in segments already narrowed by atheroscle rotic disease as well as by dilation of normal coronary arteries Our unpublished data obtained in a few patients studied intraoperatively show that coronary arterial blood flow increased 20 to 30 per cent in response to an intravenous bolus injection of 50 to 100 μg of sodium nitroprusside We therefore feel that the coronary vasodilatory effect of sodium nitroprusside probably con tributes to the improvement of the cardiovascular status in patients receiving intravenous nitro prusside therapy

No side effects were observed during this study Since sodium nitroprusside appears to be a safe and potent coronary vasodilator and the solution of sodium nitroprusside is much easier to prepare and more stable than the solution of nitrogly cerin we feel that further investigation of its applicability under certain circumstances is warranted

Summary

The effect of the intra arterial injection of 5 to 10 μg of sodium nitroprusside on the caliber of normal and diseased coronary arteries was evalu ated in 21 patients during diagnostic cardiac catheterization In addition the effect of intra

graft injection of 5 µg of the same agent on the blood flow in aorta-right coronary artery saphe nous vein bypass grafts was also evaluated intra operatively in two patients The compound in duced an increase in the caliber of both normal and stenosed coronary arteries as well as an increase of flow in the grafts Consistent with measurements of coronary flow response to sodium nitroprusside, angina pectoris which developed in four patients during cardiac catheterization was immediately relieved and the ischemic ST segment depression significantly reversed after injection of 5 to 10 µg of the drug into the left main coronary artery Within the dose range used the drug caused no significant effect on systemic blood pressure or apparently deleterious electrophysiologic changes No side effects were observed We conclude that the primary direct action of sodium nitroprusside in the human coronary artery is vasodilatory

REFERENCES

1 Page I H Corcoran A C Dustan H P and Koppanyi T Cardiovascular actions of sodium nitroprusside in animals and hypertensive patients Circulation **11** 188 1955

2 Lang K Die rhodanbildung im tierkorper Biochem Z **259** 243 1933

3 Nickerson M Antihypertensive agents and the drug therapy of hypertension *In* Goddman and Gilman editors The pharmacological basis of therapeutics ed 4 New York 1970 MacMillan Company p 728

4 Jagger P I and Braunwald E Hypertensive vascular disease *In* Wintrobe et al editors Harrison s principles of internal medicine ed 7 New York 1974 McGraw Hill Book Company Inc p 1236

5 Chatterjee K Parmley W W Ganz W Forrester J Walinsky P Crexells C and Swan H J C Hemodynamic and metabolic responses of vasodilator therapy in acute myocardial infarction Circulation **48** 1183 1973

6 Franciosa J A Guiha N H Limas C J Rodriguera E and Cohn J N Improved left ventricular functi during nitroprusside infusion in acute infarction, Lanc 1 650 1972

7 Parmley W W Chatterjee K Charuzi Y and Swa H J C Hemodynamic effects of noninvasive systol unloading (nitroprusside) and diastolic augmentation (external counterpulsation) in patients with ac myocardial infarction Am J Cardiol **33** 819 1974

8 Miller R R Vismara L A Zelis R Amsterdam E A and Mason D T Clinical use of sodium nitroprusside in chronic ischemic heart disease Circulation 51 2 1975

9 Yeh B K Gosselin A J and Worthington F X Intra arterial infusion of sodium nitroprusside for the trea *ment of severe ischemia in ergot poisoning* (In prepara tion)

10 Carliner N H Denune D P Finch C S and Gold berg L I Sodium nitroprusside treatment of ergotam ine induced peripheral ischemia J A M A 227 3 1974

11 Rowe G G and Henderson R H Systemic and coronary hemodynamic effects of sodium nitroprusside Am Heart J **87** 83 1974

12 Larsen P B Yeh B K Gentsch T O Traad E A Faraldo A R *Gosselin A J and Swaye P S* Sodium nitroprusside as a coronary vasodilator *in man* comparison of the effect of sodium nitroprusside and papaverine hydrochloride on aortocoronary saphe ou vein graft flow Ann Thorac Surg **21** 16 1976

13 Likoff W Kasparian H Lehman J S and Segal B L Evaluation of coronary vasodilators by coro ar arteriography Am J Cardiol **13** *7 1964*

14 Barner H B Kaiser G C and William V L Effect of nitroglycerin and papaverine on coronary flow in m Am Heart J *88 13 1974*

15 Eckstein R W Newberry W B McEachen *J A* a Smith G Studies of the antiadrenergic effects of nitro glycerin on the dog heart *Circulation 4 534 1951*

16 Gorlin R Brachfeld N *Macleod C* and Bopp P Effect of *nitroglycerin on the coronary circulation* in *patients with coronary artery disease or increased* lef ventricular work Circulation **19** 705 1959

17 *Brachfeld N Bozer J and Gorlin R* Action of nitroglycerin on the coronary circulation in normal an in mild cardiac sub*jects Circulation* **19** *697* 1959

18 Fam W M and McGregor M *Effect of nitroglycerin* and dipyridamole on regional coronary resistance Cir Res **22** 649 1968

Hemodynamics of supine bicycle exercise in 'normal' children

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Supine cycling is the most convenient method of imposing an exercise stress at the time of diagnostic heart catheterization As most surgery for congenital heart defects is carried out during childhood assessment of exercise hemodynamics before and after operation requires that the exercise studies be performed during childhood Near maximal exercise at the time of heart catheterization can be carried out in most children 5 to 6 years of age and older Normal hemodynamic values are not available for near maximal supine exercise in young children so that data collected over the past 12 years in 60 children with normal or nearly normal hearts are herein reviewed

Methods

Catheters were inserted in the arm veins percutaneously or by cutdown and advanced to the pulmonary artery The brachial artery at the elbow was cannulated with a No 18 Fr Cournand needle In some children the femoral vein was catheterized percutaneously as there was no suitable superficial arm vein This study was restricted to supine exercise with the Elema electric ergometer which provides a reasonably constant work load at cycling rates of 50 to 70 r p m The ergometer was calibrated at least once yearly Cardiac output was measured by the indicator dilution method with indocyamine green dye a Waters dichromatic densitometer and a Hewlett Packard cardiac output computer This system was calibrated by the dynamic method during one of the rest periods between exercises Repeat calibrations were obtained before and at the end of intense exercise in three subjects No differences were found so that only single calibrations midway through the exercise study were used in the other tests Five repeat cardiac output measurements in seven resting children gave a mean coefficient of variation of 5 per cent and in seven children exercising for 4 to 8 minutes at light to moderate work loads the mean coefficient of variation was 7 per cent

The resting measurements were obtained about 15 minutes after insertion of the catheters and about 5 minutes after placing the subjects feet on the ergometer The subjects pedaled for 3 minutes at a work load of 4 to 7 kilo pond meters per kilogram per minute (k p m /Kg /min) rested for 3 minutes and then pedaled again for 3 minutes at a work load of about 8 to 12 k p m /Kg /min After a 5 to 10 minute rest period they then pedaled at a work load of 13 to 25 k p m /Kg / min for as long as they could before exhaustion which usually occurred in 90 to 120 seconds Leg fatigue was the reason for stopping the maximal exercise in all subjects For the first two loads the subjects cycled at 60 r p m and for the final load at 60 to 70 r p m Indicator dilution curves for measuring cardiac output were obtained during the last 30 seconds of exercise and also at 20 70 and 120 seconds after the exercise had stopped

Blood samples were withdrawn from the pulmonary artery and brachial artery near the end of each exercise load placed on ice and sent to the blood gas laboratory for determination of Po_2 and pH Per cent saturation was derived from the standard oxyhemoglobin dissociation curve Blood oxygen content was obtained by multiplying hemoglobin level in grams by 1 34 and by per cent saturation Hemoglobin was determined either before the procedure or at the end and repeated measurements were not obtained

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Table I Cardiac index and stroke volume in 'normal' subjects rest and exercise

	Boys	*Girls*	*t*
Age (yr)	12 6 ± 3 5	11 8 ± 3 1	-
No of subjects	31	29	-
Resting cardiac index (L/min/M)	3 92 ± 20	4 00 ± 0 74	04
Resting SVI (ml/beat/M)	51 9 ± 5 9	45 3 ± 6 3	41
Highest steady state exercise SVI (ml/beat/M)	58 8 ± 9 7	51 8 ± 8 2	30
Highest recovery SVI (ml/beat/M)	72 2 ± 11 0	64 6 ± 11 3	26
Peak cardiac index (L/min/M²)	10 1 ± 1 75	8 6 ± 1 81	34
Maximal heart rate (beats/min)	170 ± 17	174 ± 11	10
SVI during maximal work (ml/beat/M)	55 7 ± 12 7	46 3 ± 3 1	31

SVI stroke volume index

Subjects

Over the past 10 years it has been possible to obtain data on 31 boys and 29 girls who could be classified as having essentially normal hearts After diagnostic studies were completed it was concluded that 19 of the children had innocent heart murmurs 18 had very mild pulmonary or aortic stenosis with peak systolic gradients of less than 15 mm Hg at rest and 30 mm Hg with exercise, and the remainder had catheters inserted for abdominal cerebral or pulmonary angiography for conditions that were not debilitating or likely to interfere with exercise capacity The subjects were fasting and received 1 mg per kilogram of pethedine to a maximum of 25 mg intramuscularly 1 hour before the procedure

Results

The mean values for cardiac index and stroke volume index are summarized in Table I There was no significant sex difference for resting cardiac index The mean values are not high considering the anxieties created by the test procedure and the posture supine with the feet slightly elevated on the pedals Mean resting stroke volume index was 15 per cent higher in boys than in girls

Submaximal exercise led to a variable increase in stroke volume Using the highest stroke volume recorded during the steady state exercise (one to three loads per subject) the main change in stroke index was +9 ml per beat per square meter (13 per cent) for boys and +7 ml per beat per square meter (14 per cent) for girls

The highest stroke indices were invariably recorded within the first 2 minutes after the exercise ceased The mean peak value for boys was 72 and for girls 65 ml per beat per square meter This was an increase of about 39 per cent above resting, and 23 per cent above the peak 'steady state' exercise values This interesting finding was the subject of a previous report from this laboratory [3]

The maximal heart rates were about 20 beats per minute below those found in the same subjects exercised upright on a previous occasion with the bicycle ergometer During maximal work when the subjects were straining stroke volume tended to be a little less than the value observed during previous submaximal exercise

Comparing the cardiac output to the ergometer work load for these subjects of different size and different resting cardiac outputs, the best correlation was obtained by subtracting the resting cardiac output from the exercise output These results are summarized in Table II No definite sex difference was observed The values for the younger subjects (5 to 9 years of age) were comparable to the entire group and regression equations for each group were similar Cycling against zero frictional load would be expected to increase the cardiac output above resting and the positive Y intercept confirms this in the regression equations The minimum load setting on the ergometer system in use taking friction into account was 50 k p m per minute

The 3 minute work time was deliberately chosen to reduce the time required for the study to reduce leg fatigue and because it was much easier for the younger subjects A pilot study was carried out to follow cardiac outputs during the first 6 minutes of exercise Children 6 to 14 years of age five with and nine without significant heart defects exercised at 4 to 6 k p m/kg/min

or 6 minutes and after a 5 minute rest at 10 to 12 k p m /Kg /min for 6 minutes Outputs were obtained after 1 2 4 and 6 minutes of exercise The 4 minute output was taken as 100 per cent and the other outputs were expressed as a per cent of the 4 minute value The results (Table III) showed that after only 1 minute of exercise mean cardiac output had increased to 95 per cent of the 4 minute value by 2 minutes it was 98 per cent At 6 minutes mean output was 102 per cent of the 4 minute value The outputs at 1 and 2 minutes of exercise were closer to the 4 minute value for the lighter loads compared to the heavier loads but even with exercises of about 12 k p m /Kg /min the mean output after 2 minutes of supine exercise was 93 per cent of the 4 minute value For clinical studies in children there would seem to be little to be gained by prolonging exercise past 3 minutes

The mean pulmonary artery Po during maximal exercise was 24 to 25 mm Hg for two age groups of boys and younger girls but was 27 7 mm Hg for the older girls (Table IV) Mixed venous pH fell to values between 7 21 and 7 26 Mean mixed venous oxygen saturation was 33 to 41 per cent higher than that calculated for maximal upright exercise in children by Eriksson and co workers

The mean pressures in the pulmonary and brachial arteries during maximal exercise are given in Table V Mean pulmonary artery pressure was 24 mm Hg and mean systemic pressure was 112 to 115 mm Hg No sex or age difference was observed

Discussion

In the diagnostic heart catheterization laboratory oxygen uptake ($\dot{V}o_2$) is not an easily measurable parameter in young children either at rest or during exercise for considerable attention needs to be paid to small details in collecting expired air More than lip service should be given to the steady state requirement of the Fick principle when oxygen uptake and A V oxygen differences are used to calculate cardiac output While not without its own drawbacks the indicator dilution method is easier to use because complete air collection is not required the measurement requires only 10 seconds so that a steady state is not mandatory and the duration of exercise can therefore be shorter The indicator dilution

Table II Increase in cardiac output above resting for various steady state work loads normal subjects*

Work load (k p m /min)	Ages 5 to 15 yr (n = 80)		Ages 5 to 9 yr (n = 24)	
	No	$\Delta\dot{Q}$ L /min	No	$\Delta\dot{Q}$ L /min
100	10	2.06 ± 0 85	6	1 93 ± 0 73
1 0	17	2.93 ± 0 65	12	2 90 ± 0 51
220	3	2 46 ± 1 06	3	2 46 ± 1 06
2 6	32	3 63 ± 1 16	7	4 30 ± 0 78
333	11	3 28 ± 0 96	6	3 41 ± 1 03
390	16	5 11 ± 1 07	5	5 27 ± 0 45
510	16	5 94 ± 1 74	5	5 72 ± 1 03
550	3	6.47 ± 2 12		—
630	14	5 94 ± 1 4		—
50	9	8.83 ± 2 06		—

All subjects, $\Delta\dot{Q}$ = 1.03 + 0 00946 work load in k p m /min S D = 1 34 r = 0 80 5 to 9 year olds $\Delta\dot{Q}$ = 1 19 + 0 00901 work load in k p m /min S D = 0 8 r = 0 9 Q cardiac output in L /min Δ, increase in cardiac output above resting i.e. Q exercise – Q rest S D standard deviation correlation coefficient

Table III Time course of cardiac output for supine exercise

Time (min.)	Cardiac output as per cent of 4 min value	
	4 to 6 k p m /Kg /min	8 to 12 k p m /Kg min
1	95 ± 11 (10)	90 ± 7 (10)
2	98 ± 10 (14)	93 ± 10 (14)
6	102 ± 7 (11)	102 ± 8 (10)

Numbers in parentheses indicate the numbers of subject

method allows measurement of cardiac output during maximal exercise where a steady state is not obtained and the method allows repeat measurements every 15 to 20 seconds

The fit adult has difficulty in telling the difference between 200 and 300 k p m per minute work loads whereas to the child of 15 kilograms this is the difference between a load he can sustain for 10 minutes and a load he can barely cycle against for a minute A satisfactory correlation between cardiac output and work load even at these small work loads indicates that work load is a reasonable substitute for $\dot{V}o_2$ as the reference source for exercise studies Reeves and co workers found the cardiac output response to mild supine exercise to be nonlinear in adult subjects but such

Table IV Pulmonary artery blood P_{O_2} and pH near fatigue point with supine exercise

	Age	Po_2 (mm Hg)	pH	Per cent sat	Hb Gm./100 ml
Males	< 12	24 0 ± 2 8	7 25 ± 0 04	33 4 ± 7 3	11 8 ± 1 2
	13 16	24 5 ± 1 8	7 21 ± 0 04	32 0 ± 4 4	14 4 ± 0 7
Females	< 12	24 6 ± 1 7	7 26 ± 0 03	3₅ 5 ± 3 1	1?1 ± 1 2
	13 16	27 7 ± 3 9	7 26 ± 0 03	41 0 ± 10 2	13 2 ± 0 8

Table V Pulmonary and brachial artery pressures during near maximal supine exercise

	PA (mm Hg)			BA (mm Hg)		
	Systole	Diastole	Mean	Systole	Diastole	Mean
Males	36 ± 6	13 ± 2	24 ± 6	190 ± 21	84 ± 9	115 ± 5
Females	3? ± 6	13 + 5	24 ± 5	176 ± 23	81 ± 9	112 ± 10

PA pulmonary artery BA brachial artery

was not the case for the children of this report The efficiency of steady state bicycle ergometer exercise work of 200 to 1 500 k p m per minute in children varies from 20 to 23 5 per cent [7] the same as in adults [8] Unpublished data from this labora tory using 11 to 14 year old boys as subjects indicated that there was no difference in the Vo for submaximal exercise of children exercising either supine or upright [7] and this is also true for adult subjects

The maximal heart rates were well below those reported for normal children Maximum heart rates during supine exercise are known to be 10 to 15 beats per minute lower than for upright exer cise in healthy young adults [9, 10] Values in young children have not been published Without any sedations or instrumentation a group of 20 normal boys aged 8 to 15 years had maximal heart rates 9 ± 6 beats per minute lower for supine compared to upright bicycle exercise[7] (upright 196 supine 187) One factor leading to the lower maximal heart rates in the present study was the short duration of maximal exercise We were dependent on the motivation of unselected subjects to perform maximal work and this is a difficult factor to assess However, the subjects were verbally pushed until they could no longer cycle The mechanical problem facing the young child to get enough leverage to cycle against a stiff braking force while lying supine and having one arm fixed out on an arm board and not available for hanging on was an added factor

Technicians supported the shoulders where necessary Doll and Keul[14] found the Po_2 of blood from the femoral veins of young adults during maximal supine exercise to fall to 19 mm Hg The Po_2 of the mixed venous blood of our subjects fell to 25 mm Hg, which suggests that near maximal work was being performed

Values reported in the literature for cardiac index using the bicycle ergometer and dye dilu tion methods are summarized in Table VI In prepubertal children Eriksson[11] found peak cardiac index values of 9 2 L per minute pe square meter, increasing to 10 3 after training Postpubertal boys and adult males of above average fitness had slightly higher mean values of 11 3 [4, 1] For young women Astrand and co work ers[13] found similar peak values of 10 8 L pe minute per square meter but these subjects were of above average fitness For supine exercise th data of Stenberg and co workers[9] are comparable and peak cardiac index was 11 3 in healthy t young adults The peak mean cardiac index in th male subjects of this report was 10 1 very simila to the upright and supine values listed above Th mean peak cardiac index in the girls presente here was about 15 per cent lower than in the boy The children from the present investigation we less accustomed to exercise than the children ar young adults of the above Swedish studies y the cardiac stroke volume indices were qui similar

While the practice of converting cardiac outpu or stroke volume measurements to an index base on surface area can be debated, this is one o many ways to correct for differences in body siz Body weight, lean body mass or height raised to power between 1 6 and 3 have been suggested a alternatives

The stroke volume index for the boys in th study was similar to the values in the literatu for maximal upright exercise, but 13 per ce below values for supine exercise reported by Ste berg and co workers[9] in fit young adult men

Table VI Cardiac index and stroke index during maximal exercise values from literature

Author Ref No	No	Sex	Mean age	CI† L/min/M	SVI† ml/M	Heart rate	Posture	Fitness
1	9	M	1?	9?	49	187	U†	Av†
1	9	M	1?	10 3	57	185	U	+†
	8	M	14	11 4	56	201	U	+
2	17	M	23	11 4	5?	196	U	+
3	11	F	21	10 8	5?	194	U	+
	6	M	?6	11 3	64	180	S†	+
Present study	31	M	1?	10 1	56	1 0	S	Av
Present study	29	F	1?	8 6	46	1?4	S	A?

Sam subjects after training.
CI, cardiac index SVI strok olume index U pright S supine Av verag + abo e rage

The cardiac output/work load relationship in our subjects compared favorably to available values in the literature for young adults doing supine work. The values were slightly below those reported by Grimby and Nilsson for 900 k p m per minute possibly because longer work periods were used by these authors

The subtraction of the resting cardiac output from the exercise outputs has the potential fault that the initial resting value may be falsely high because of anxiety If intense anxiety is present a more accurate resting value may be obtained 15 to 20 minutes after the exercise is completed The close relationship between work load and cardiac output and work load and Vo obviates the need for Vo measurements None of the subjects included in this report were restricted in any way from participation in sports or physical education although it must be admitted that the parents may have subconsciously imposed some restrictions because of actual or suspect heart disease

Hemoconcentration is known to occur during exercise and it would have been more suitable to systematically measure blood hemoglobin concentration at rest and during each level of exercise This was not done although presumably the short duration of most of the exercise tests would have prevented much change in blood hemoglobin About 20 indicator curves and calibrating curves were obtained during the studies with the infusion of up to 200 ml of normal saline and this would have reduced if not reversed any tendency to hemoconcentration

The results show that exercise studies can be obtained in the diagnostic heart catheterization laboratory in children 5 years of age and over and this includes near maximal exercise Normal data are provided for subsequent comparison with heart patients

Summary

Sixty children age 5 to 16 years with normal or nearly normal hearts performed submaximal and maximal supine bicycle exercise Submaximal cardiac output was linearly correlated with work load (r = 0 80) After 2 minutes exercise cardiac output was over 90 per cent of the value for 6 minutes exercise Maximal cardiac index was 10 1 ± 1 8 for boys and 8 6 ± 1 8 L per minute per square meter for girls Stroke volume was highest during the recovery period after maximal exercise Pulmonary artery Po_2 fell to 24 mm Hg oxygen saturation to 33 per cent and pH to 7 21 During maximal exercise mean pulmonary artery pressure was 24 ± 5 mm Hg and mean brachial artery pressure was 113 ± 8 There were no major differences between children aged 5 to 9 years of age and those 10 to 16 years except for higher hemoglobin values in postpubertal children

REFERENCES

1 Cumming G R and Alexander W D The calibration of bicycle ergometers, Can J Physiol Pharmacol 46 31, 1968
2 Shinebourne E Fleming J and Hamer J Calibration of indicator dilution curves in man by the dynamic method, Br Heart J 29 920 196,
3 Cumming G R Stroke volume during recovery from supine bicycle exercise J Appl Physiol 32 575 197?
4 Eriksson B O Grimby G and Saltin B Cardiac output and arterial blood gases during exercise in prepubertal boys J Appl Physiol 31 348 1971
5 Visscher M B and Johnson J A Fick principle Analysis of potential errors in its conventional application J Appl Physiol 5 635 1953
6 Reeves J J Grover R F Folley G F and Blount S G Jr Circulatory changes during mild supine exercise J Appl Physiol 16 279 1961
7 Cumming G R Unpublished data

Table IV Pulmonary artery blood P_{O_2} and pH near fatigue point with supine exercise

	Age	*Po_2 (mm Hg)*	*pH*	*Per cent sat*	*Hb Gm /100 ml*
Males	< 12	24 0 ± 2 8	7 25 ± 0 04	33 4 ± 7 3	11 8 ± 1 2
	13 16	24 5 ± 1 8	7 21 ± 0 04	32 0 ± 4 4	14 4 ± 0 [illegible]
Females	< 12	24 6 ± 1 7	7 26 ± 0 03	35 5 ± 3 1	1? 1 ± 1 2
	13 16	27 7 ± 3 9	7 26 ± 0 03	41 0 ± 10 2	13 ? ± 0 8

Table V Pulmonary and brachial artery pressures during near maximal supine exercise

	PA (mm Hg)*			*BA (mm Hg)*		
	Systole	*Diastole*	*Mean*	*Systole*	*Diastole*	*Mean*
Males	36 ± 6	13 ± 2	24 ± 6	190 ± 21	84 ± 9	115 ± 5
Females	35 ± 6	13 ± 5	24 ± 5	176 ± 23	81 ± 9	112 ± 10

PA pulmonary artery BA brachial artery

was not the case for the children of this report The efficiency of steady state bicycle ergometer exercise work of 200 to 1 500 k p m per minute in children varies from 20 to 23 5 per cent [7] the same as in adults [8] Unpublished data from this laboratory using 11 to 14 year old boys as subjects indicated that there was no difference in the Vo_2 for submaximal exercise of children exercising either supine or upright,[7] and this is also true for adult subjects

The maximal heart rates were well below those reported for normal children Maximum heart rates during supine exercise are known to be 10 to 15 beats per minute lower than for upright exercise in healthy young adults [9, 10] Values in young children have not been published Without any sedations or instrumentation a group of 20 normal boys aged 8 to 15 years had maximal heart rates 9 ± 6 beats per minute lower for supine compared to upright bicycle exercise[7] (upright 196, supine 187) One factor leading to the lower maximal heart rates in the present study was the short duration of maximal exercise We were dependent on the motivation of unselected subjects to perform maximal work and this is a difficult factor to assess However the subjects were verbally pushed until they could no longer cycle The mechanical problem facing the young child to get enough leverage to cycle against a stiff braking force while lying supine and having one arm fixed out on an arm board and not available for hanging on was an added factor

Technicians supported the shoulders where necessary Doll and Keul[14] found the Po_2 of blood from the femoral veins of young adults doing maximal supine exercise to fall to 19 mm Hg The Po of the mixed venous blood of our subjects fell to 25 mm Hg which suggests that near maximal work was being performed

Values reported in the literature for cardiac index using the bicycle ergometer and dye dilution methods are summarized in Table VI In prepubertal children Eriksson[11] found peak cardiac index values of 9 2 L per minute per square meter increasing to 10 3 after training Postpubertal boys and adult males of above average fitness had slightly higher mean values of 11 3 [4, 12] For young women Astrand and co workers[13] found similar peak values of 10 8 L per minute per square meter but these subjects were of above average fitness For supine exercise the data of Stenberg and co workers[9] are comparable and peak cardiac index was 11 3 in healthy fi young adults The peak mean cardiac index in the male subjects of this report was 10 1 very simila to the upright and supine values listed above Th mean peak cardiac index in the girls presente here was about 15 per cent lower than in the boy The children from the present investigation wel less accustomed to exercise than the children an young adults of the above Swedish studies y the cardiac stroke volume indices were qui similar

While the practice of converting cardiac outpu or stroke volume measurements to an index base on surface area can be debated this is one many ways to correct for differences in body siz Body weight lean body mass or height raised to power between 1 6 and 3 have been suggested alternatives

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Transposition of the great arteries, primum atrial septal defect, azygos continuation of the inferior vena cava, bilateral superior venae cavae, and dextrocardia with centrally placed liver

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Patients with transposition of the great arteries and no associated lesions other than atrial septal defect are being successfully treated by Mustard's operation. Patients with complex forms of transposition of the great arteries still present a diagnostic and surgical challenge.[1]

The association of transposition of the great arteries with dextrocardia and indeterminate situs is rare. Shaher[6] found only one case of a primum atrial septal defect with transposition of the great arteries in a series of 178 cases. Bilateral superior venae cavae were present in four cases in her series. In our own series of 386 Mustard operations only five patients had bilateral superior venae cavae.

We present here a case of transposition of the great arteries with ostium primum atrial septal defect, dextrocardia, azygos continuation of the inferior vena cava to right superior vena cava, bilateral superior venae cavae and direct drainage of the hepatic veins to right and left atrium which was successfully treated by Mustard's operation.

Case report

A three-year-old girl was admitted to the Hospital for Sick Children, Great Ormond Street, in February 1966. Cyanosis had been noted at twenty months of age. On examination there was Grade II cyanosis. The liver was not enlarged. There was Grade 3/6 systolic murmur at the left sternal edge. The second sound was loud and single. Her hemoglobin was 14.6 Gm per cent, hematocrit 48 per cent. Howell-Jolly bodies were not seen. The electrocardiograms demonstrated dextrocardia, prolonged P-R interval, and "anterior ventricular hypertrophy." Chest x-ray showed dextrocardia, slight cardiac enlargement, increased pulmonary vascularity, and centrally placed liver.

Cardiac catheterization and angiocardiogram established the diagnosis of dextrocardia and single atrium (Table I). Because of the complex nature of the abnormalities and her good clinical condition, it was decided to continue to observe this child.

The patient was readmitted in June 1971 for investigation as her cyanosis had increased, although her exercise tolerance remained unchanged. Her hemoglobin was 1? 6 Gm per cent, hematocrit 51 per cent. Chest x-ray at this time showed normal lung fields and some cardiac enlargement.

Electrocardiography demonstrated prolonged P-R interval, dextrocardia, and biventricular hypertrophy. The mean frontal P wave axis varied on different recordings from +80 to +1 0. Repeat cardiac catheterization and angiocardiogram (Table I) revealed dextrocardia, transposition of the great arteries, centrally placed liver, azygos continuation of the inferior vena cava and bilateral superior venae cavae with a communication vein. The possibility of total anomalous pulmonary venous drainage into the systemic venous atrium with obstruction was raised (pulmonary vein mean pressure 20 mm Hg and systemic atrium mean pressure 7 mm Hg). Both superior venae cavae and the hepatic veins appeared to drain into the systemic venous atrium.

The patient's condition deteriorated during the intervening months and it was decided to operate on May 11, 19 ?, by which time she was nine years of age. The heart was exposed through a median sternotomy incision. The external appearances were consistent with transposition of the great arteries and dextrocardia. The morphological right atrial

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8 Åstrand I Aerobic work capacity in men and women with special reference to age Acta Physiol Scand 49(Suppl) 169 1960
9 Stenberg J Astrand P O Ekblom B Royce J and Saltin B Hemodynamic response to work with different muscle groups sitting and supine J Appl Physiol 22 61 1967
10 Bevegard S Fryschuss U and Strandell T Circulatory adaption to arm and leg exercise in supine and sitting position J Appl Physiol 21 37 1966
11 Eriksson B O Physical training oxygen supply and muscle metabolism in 11 13 year old boys Acta Physiol Scand Suppl vol 61 384 1972
12 Ekblom B Astrand P O Saltin B Stenberg J and Wallstrom B Effect of training on circulatory response to exercise J Appl Physiol 24 518 1968
13 Astrand P O Cuddy T E Saltin B and Stenberg J Cardiac output during submaximal and maximal work J Appl Physiol 19 268 1964
14 Doll E and Keul J Zum Stoffwechsel des Skeletmuskels II Sauerstoffdruk Kohlensauerdruck pH standard Bicarbonet und base Excess in venosen Blut der arbeitendern Muskulatur Untersuhungen an Hochleistungssportlern Pfluegers Arch 301 214 1968
15 Grimby G and Nilsson N J Cardiac output during exercise induced pyrogen fever Scand J Clin Lab Invest 15(Suppl 69) 44 1963

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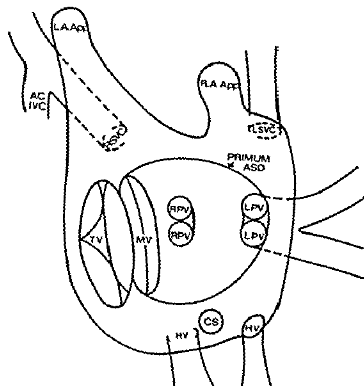


Fig 1A and B *A* diagram of the heart of an 8 year old girl patient showing a large primum ASD Abbreviations AC IVC = azygos continuation of the inferior vena cava LA = left atrium RA = right atrium App = appendage R SVC = right superior vena cava L SVC = left superior vena cava ASD = atrial septal defect RPV = right pulmonary vein LPV = left pulmonary vein TV = tricuspid valve MV = mitral valve HV = hepatic vein CS = coronary sinus ⟶ indicates flow of oxygenated blood from the pulmonary veins to the tricuspid valve → indicates flow of venous blood to the mitral valve For explanation see text

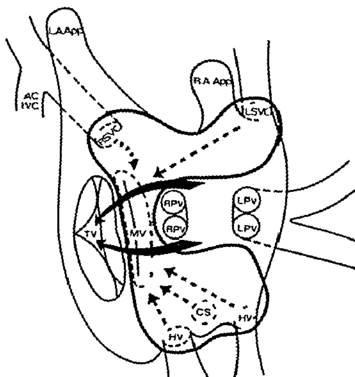


Fig 1B Diagram showing suturing of Dacron patch around the systemic veins coronary sinus and hepatic veins (See text) Abbreviations as in *Fig 1A*

Table I Cardiac catheterization

	Feb 4 1966		*June [illegible]*	
	O Saturation pressures		*O S[illegible] pressures*	
	(%)	(mm Hg)	(%)	(mm [illegible])
Superior vena cava				
Right vena cava			53	[illegible] (mean)
Left vena cava			53	
Right atrium	63	2	80	8
Right ventricle	86	88/5	86	100 5?
Aorta	81	88/50	70?	100 [illegible]
Pulmonary artery	—	—	86	50 35
Left ventricle	82	42/2	85?	60 6
Left atrium	—	—	—	—
Pulmonary veins	—	—	—	[illegible] (mean)

Table II Intraoperative pressures

	Pre operative	*Post operative*
Aorta	100/80	100 80?
Right ventricle	95 100/10	95-100 10
Left ventricle	45/5	35-40 5
Left atrium (pulmonary venous)	6	15
Right atrium (systemic venous)	3	13
Left superior vena cava		13

appendage was on the left connected to the left sided right atrium Left and right superior venae cavae drained into the right atrium (Table I) The left atrium was located posteriorly and slightly to the right Its appendage had a morphology of the left atrial appendage The ascending aorta and right atrium were cannulated A vent was placed into the right ventricle

On bypass the child was cooled to 19 C nasopharyngeal temperature and the aorta was cross clamped The blood was drained to the oxygenator and the right superior vena cava left superior vena cava and both hepatic veins were occluded The right atrium was then opened and the anatomy identified The one hepatic vein drained into the right atrium and the other into the left atrium The coronary sinus was in the right atrium The left superior vena cava was in the typical position for dextrocardia close to the right atrial appendage The right superior vena cava was behind the heart attached to the posterior aspect of the left atrium The pulmonary veins drained into the left atrium The inferior vena cava continued as an azygos vein and opened into the right superior vena cava There was a large primum atrial septal defect (Fig 1A)

Part of the atrial septum was excised and a large patch of two way stretch Dacron measuring approximately 10 × 14 cm was placed into the atrium It was sutured around the systemic veins coronary sinus and hepatic veins as illustrated in Fig 1B It was sutured inferiorly to the superior aspect of the ventricular septum between the two A V valves In this

1/ 93

y systemic venous blood was redirected through the uspid valve to the right ventricle and aorta After seventy nutes of circulatory arrest bypass was restarted and the ient rewarmed Cardiopulmonary bypass was discontinued hout difficulty and the heart took over readily The pre d postoperative pressures are given in Table II

The postoperative course was uncomplicated The patient entilated on the Engstrom Ventilator for 36 hours She s discharged home on the twelfth postoperative day At at time her hemoglobin was 1? 6 Gm per cent and PVC 36 r cent The electrocardiogram showed sinus rhythm and olonged PR interval as before the operation At the la t itpatient visit on April 14 1975 she was asymptomatic est x ray was within normal limits the electrocardiogram owed sinus rhythm and she was on no medication

iscussion

Anomalies of systemic venous drainage can resent an additional technical challenge in atients with complex congenital heart defects [1] he technique of deep hypothermia and circulatory arrest was the obvious solution to the difficult problem of multiple venous cannulation ardiac repair was complicated by the distances between the orifices of systemic veins and also by he presence of primum rather than secundum itrial septal defect Superficial stitches carefully placed in the area between the mitral and ricuspid valve were used to avoid injury to the onduction mechanism Intracardiac electrical location of the bundle of His was not possible because of the use of deep hypothermia and circulatory arrest

This report confirms that complex anomalies can be safely corrected Precise diagnosis and careful planning of surgical techniques are essential

Summary

Successful surgical correction of transposition of the great arteries in a nine year old girl with dextrocardia primum atrial septal defect bilateral venae cavae and azygos continuation of inferior vena cava is reported The patient was cooled on cardiopulmonary bypass and the operation performed under circulatory arrest at 19° C nasopharyngeal temperature The problems of diagnosis and management are discussed

REFERENCES

1 Danielson G K Mair D D Ongley R A and McGoon D C Repair of transposition of the great arteries by transposition of the venous return Surgical considerations and results of operations J Thorac Cardiovasc Surg 61 96 1971
2. Clarkson P M, Barratt Boyes B G Neutz J M and Lowe J B Results over a ten year period of palliation followed by complete surgery for transposition of the great arteries Circulation 45 1251 1972
3 Breckenridge I M, Oelert H Stark J Graham C R Bonham Carter R E and Waterston D J Mustard operation for transposition of the great arteries A review of 200 cases Lancet 1 1140 1972
4 Champsaur G L, Sokol D M Trusler G A, and Mustard W T Repair of transposition of the great arteries in 123 paediatric patients Circulation 47 1032 1973
5 Lindesmith G G Stiles Q R, Tucker B L Gallaher M E Stanton R E, and Meyer B W The Mustard operation as a palliative procedure J Thorac Cardiovasc Surg 63 75 1972
6 Stark J de Leval M R Waterston D J, Graham G R and Bonham Carter R E Corrective surgery of transposition of the great arteries in the first year of life J Thorac Cardiovasc Surg 67 673 1974
7 Rastelli G C McGoon D C and Wallace R B Anatomic correction of transposition of the great arteries with ventricular septal defect and sub-pulmonary stenosis, J Thorac Cardiovasc Surg 58 545 1969
8 Kirklin J W Barcia A Deverall P B Kouchoukos N T and Bargeron L M Jr Surgical treatment of complex forms of transposition Br Heart J 33 (Suppl) 73 1971
9 Paul W M Van Praagh S and Van Praagh R Transposition of the great arteries chapter 40 in Paediatric Cardiology ed H Watson London 1968 Publ Lloyd Luke pp 5 6
10 Shaher R M Complete transposition of the great arteries London and New York 1973 Academic Press, p 162
11 de Leval M Ritter D G McGoon D C and Danielson G K Anomalous systemic venous connection Surgical considerations Mayo Clin Proc 50 599 1975

Severe papillary muscle dysfunction substantiated by atrial pacing during cardiac catheterization

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Fluctuating mitral regurgitation due to papillary muscle dysfunction was first described by Burch and co workers[1] in 1963 Numerous reports subsequently have documented the acute hemodynamic alterations of this syndrome [2-4] This case illustrates that atrial pacing is another means of provoking papillary muscle dysfunction to confirm the diagnosis

Case report

A 70 year old woman was admitted in 1971 with diverticulitis and a perforated sigmoid diverticulum which required a sigmoid colectomy for relief Postoperatively the patient experienced an acute inferior wall myocardial infarction from which she recovered without incident She was hospitalized four times in the next 3 years Three of these admissions were for prolonged chest pain two were associated with myocardial infarctions involving the inferior and anterolateral walls of the left ventricle and one admission was for acute pulmonary edema

In June 1975 the patient was admitted with a 4 week history of nocturnal angina pectoris and dyspnea She was in congestive heart failure on admission and was treated appropriately A Grade 3/6 holosystolic murmur was heard at the cardiac apex on initial physical examination Chest roentgenogram showed an enlarged left ventricle and pulmonary vascular congestion An electrocardiogram demonstrated interventricular conduction delay and nonspecific T wave changes

Serial studies remained stable and did not suggest acute cardiac injury Acute papillary muscle dysfunction was considered to be the best explanation for the patient s nocturnal dyspnea

The baseline cardiac output (thermodilution method) and simultaneous left ventricle end diastolic pressure (LVEDP) and pulmonary artery wedge pressures (PAWP) recorded at cardiac catheterization are shown in Table I Left ventricular cineangiography in the right anterior oblique projection demonstrated an akinetic inferior wall and normal motion of the anterior and apical walls Mild mitral regurgitation was noted Immediately after the left ventriculogram simultaneous left ventricle end diastolic and pulmonary artery wedge pressures were 11 and 6 mm Hg mean respectively (see Table I)

Atrial pacing at a rate of 120 beats per minute was then initiated After 5 minutes of pacing the patient developed mild angina pectoris Simultaneous LVEDP and PAWP contours at this time are illustrated in Fig 1 After 11 minutes of atrial pacing the pulmonary artery wedge pressure dramatically increased to a mean of 22 mm Hg (A wave 20 mm Hg V wave 30 mm Hg) A repeat left ventricular cineangiogram was performed at this time During the left ventricular injection the V wave in the pulmonary artery wedge pressure contour increased further Simultaneous PAWP and LVEDP tracings immediately after the second left ventricular cineangiogram are illustrated in Fig 2 The previously mild mitral regurgitation observed on angiography had now become severe The patient immediately complained of increasing chest tightness and shortness of breath She was given sublingual nitroglycerin and was relieved of her symptoms as the previously abnormal pressures returned to pre stress levels (Figs 3 and 4 and Table I)

Coronary cineangiography was subsequently performed The right coronary artery was totally occluded in its proximal portion The right posterior descending artery was filled by collaterals from the left anterior descending and proximal circumflex arteries The left anterior descending artery was a large vessel with a 95 per cent narrowing just proximal to the first septal perforating branch The circumflex artery was totally occluded just distal to the first marginal branch

In view of the patient s uncontrolled increase in cardiac symptoms and on the basis of findings at cardiac catheterization aortocoronary bypass and mitral valve replacement surgery were recommended to the patient

At operation old lateral and inferior wall scars of the left ventricle were seen The mitral valve annulus and leaflets appeared normal Both papillary muscles had large amounts of yellowish white tissue within them and the chordae tendineae were long and slightly redundant A double aortocoronary bypass was performed with saphenous vein grafts to

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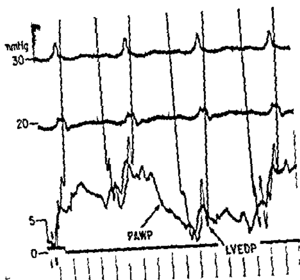


Fig 1 Simultaneous left ventricular end diastolic pressure (LVEDP) and pulmonary artery wedge pressure (PAWP) after 5 minutes of atrial pacing at 170 beats per minute Note the absence of a large V wave in the PAWP tracing (paper speed 100 mm per second)

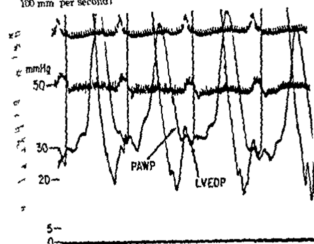


Fig 2 Simultaneous pulmonary artery wedge pressure (PAWP) and left ventricular end diastolic pressure (LVEDP) after atrial pacing and initiation of a second LV cineangiogram Note the elevated pressures and the large V wave in the PAWP tracing

the distal posterior descending and left anterior descending arteries Significant mitral regurgitation was apparent at surgery and initially mitral valve annuloplasty was attempted to relieve this The annuloplasty did not relieve the mitral regurgitation however and it was necessary to replace the mitral valve with a Hancock prosthesis

The patient's postoperative course was marked by severe neurologic dysfunction seizures and renal failure She died 9 days after surgery Gross pathologic findings were of an old inferior left ventricular wall myocardial infarction an acute lateral wall myocardial infarction and cerebral edema

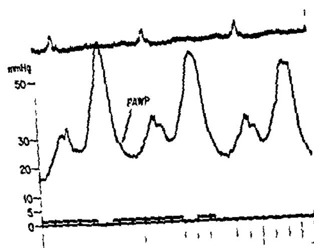


Fig 3 Pulmonary artery wedge pressure tracing (PAWP) 30 seconds after sublingual nitroglycerin Marked mitral regurgitation is still present as demonstrated by the large V wave in the PAWP tracing

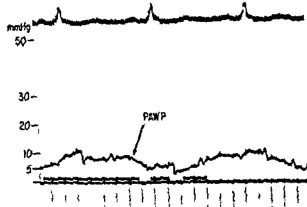


Fig 4 PAWP tracing 60 seconds after sublingual nitroglycerin Note the dramatic fall in wedge pressure at this time

Discussion

This is the first reported case of a patient with papillary muscle dysfunction in whom severe acute mitral regurgitation was purposely provoked by atrial pacing at cardiac catheterization Brody and Criley described a patient with intermittent papillary muscle dysfunction who developed severe mitral regurgitation spontaneously at catheterization The mitral regurgitation was relieved by sublingual isosorbide dinitrate (Isordil) More recently there have been two reports describing the induction of papillary muscle

Table I Cardiac catheterization data before and after atrial pacing and left ventricle cineangiography

	Baseline resting state	*After LV cine No 1*	*After atrial pacing (11 min)*	*After LV cine No 2 + atrial pacing*	*After dose of nitroglycerin*
Cardiac output (L/min)	3 06	—	—	2 86	3 94
LVEDP (mm Hg)	5	11	—	30	8
PAWP (mm Hg)	5 mean	6 mean	A 20 V 30 22 mean	A 35 V 63 40 mean	5 mean

dysfunction at catheterization One patient developed severe mitral regurgitation during bicycle ergometry[3] and the other patient developed severe mitral regurgitation during phenylephrine infusion[4]

Our patient s history suggested severe mitral regurgitation due to acute papillary muscle dysfunction She described waking at night acutely short of breath with angina pectoris She would get complete relief of her symptoms by sitting up in bed and taking nitroglycerin She rarely experienced angina pectoris or dyspnea during the day

Cardiac catheterization confirmed the clinical impression of papillary muscle dysfunction After the stress of atrial pacing and the second left ventricular cineangiogram the left heart pressure rose precipitously (Fig 2) Sublingual nitroglycerin relieved the patient s symptoms and allowed the abnormal pressures to return to pre stress levels (Fig 4) The prompt response to nitroglycerin suggested that preload reduction may have played the primary role in relieving the acute mitral regurgitation in this case The latter explanation would be consistent with experimental findings which show that papillary muscle infarction alone will not cause mitral regurgitation unless there is associated abnormal myocardium surrounding the affected papillary muscle[6] We believe that the papillary muscle dysfunction in our patient was induced by atrial pacing causing ischemia of the papillary muscle and surrounding left ventricular myocardium This effect was probably aggravated by the myocardium depressing influence of the angiographic contrast medium

In summary our patient had episodes of acute pulmonary edema secondary to ischemia of the papillary muscle and surrounding myocardium Resulting papillary muscle dysfunction caused severe mitral regurgitation which could be relieved with sublingual nitroglycerin This hypothesis originally suggested by Burch and associates[1] was supported by our findings at cardiac catheterization

Summary

A patient experienced episodic pulmonary edema accompanying nocturnal angina pectoris The symptoms were provoked at cardiac catheterization by atrial pacing Simultaneous onset of chest pain shortness of breath and sudden appearance of a large V wave in the pulmonary artery wedge pressure contour confirmed acute mitral valve regurgitation Rapid reversal of these changes after nitroglycerin administration supported papillary muscle dysfunction as the explanation for these hemodynamic changes

REFERENCES

1 Burch G E DePasquale N P and Phillips J H Clinical manifestations of papillary muscle dysfunction Arch Intern Med **112** 112 1963
2 Brody W and Criley J M Intermittent severe mitral regurgitation N Engl J Med **283** 673 1970
3 Bauman D J and Sutton R B Unusual hemodynamic response during exercise induced angina pectoris Chest **68** 365 1975
4 Markiewicz W Amikam S Roguin N and Riss E Changing haemodynamics in patient with papillary muscle dysfunction Br Heart J **37** 445 1975
5 Flaherty J T Reid P R Kelly D T Taylor D R Weisfeldt M L and Pitt B Intravenous nitroglycerin in acute myocardial infarction Circulation **51** 132 1975
6 Mittal A K Langston M Jr Cohn K E Selzer A and Kerth W J Combined papillary muscle and left ventricle wall dysfunction as a cause of mitral regurgitation An experimental study Circulation **44** 174 1971
7 Roberts W C and Cohen L S Left ventricular papillary muscles Description of the normal and a survey of conditions causing them to be abnormal Circulation **46** 138 1972

echanical factors and the electrocardiogram

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ıechanıcal factors play a sıgnıficant role ın the appearance of the surface electrocardıogram ECG) Although a number of papers have ap ı on varıous aspects of the subject there has en no comprehensıve revıew and no attempt to these factors (see Table I) With ıncreasıng applıcatıon of transvascular probes to the ınsıde of heart chambers the correct ıntrepre tatıon of mechanıcally ınduced arrhythmıas becomes more pressıng Several revıews of pace nduced arrhythmıas have appeared ıt wıth no mentıon of mechanıcal factors A gy monograph on ıntrınsıc rate regula tıon publıshed by Jensen ın 1971 dıscusses mechanıcal factors regulatıng cardıac rate and ıncludes rhythm dısturbances caused by cardıac catheters but no reference ıs made to artıfıcıal pacemakers or mechanıcal effects other than rtınent to rate regulatıon The purpose of revıew ıs to suggest that mechanıcal effects are ubıquıtous and must be consıdered along wıth other etıologıes ın a wıde varıety of ECG manıfes tatıons. Although some of the conclusıons below may be consıdered speculatıve as well as the explanatıons for some of the ıllustratıve ECG s they are more reasonable than alternatıve elec trophysıologıc explanatıons. Interest ın thıs topıc was fırst aroused by the growıng body of lıtera ture on Wedensky phenomena ın the human heart (see below) and the realızatıon that many of the ECG s ıllustratıng these effects could easıly and alternatıvely be explaıned by mechanıcal and mechanıcal electrıcal summatıon effects

A External factors

In analyzıng mechanıcal factors external to the heart ıtself that ınfluence the ECG ıt may be appropnate to start wıth the artıfactual ECG recorded durıng closed chest massage ın the absence of ıntrınsıc cardıac electrıcal actıvıty[4] Although the genesıs of thıs artıfact ıs not entıre ly clear ıts vector ıs superıorly dırected ın the frontal plane and orıented anterıorly ın the horı zontal plane The artıfact may be used to tıme the duratıon and roughly estımate the forcefulness of the sternal compressıon The authors suggest that "ıf the heart ıs consıdered a dıpole wıth posıtıve and negatıve charges on the epıcardıal and endocardıal surfaces respectıvely then the motıon of the heart ın relatıon to the recordıng electrode would be expected to produce detect able changes of potentıal Skaaland[5] however produced artıfacts wıth chest poundıng ın deceased ındıvıduals both before and after removal of the heart from the chest cavıty Machıne compressıon of the thorax causes a square wave artıfact Lead aV_F ıs the lead that best records thıs phenomenon Poor massage results ın absent or mınımal artıfacts but larger amplıtude artıfacts do not necessarıly guarantee an adequate resuscıtatıve effort

Thumpıng as opposed to compressıng the chest ıs a long standıng rıtual as a prelımınary effort to termınate cardıac arrest In a recent study on anoxıc dogs chest thumpıng ın the presence of anoxıc standstıll dıd not provıde adequate perıph eral cırculatıon Although ıt occasıonally termı nated ventrıcular tachycardıa and restored sınus rhythm ıt just as frequently caused ventrıcular fıbrıllatıon or ırreversıble standstıll Ventrıcular fıbrıllatıon ın these dogs was not ınfluenced by sıngle or multıple thumps The authors advıse agaınst thumpıng unless defıbrıllatıon equıpment ıs at hand Others however have had success wıth thumpıng maıntaınıng patıents wıth Adams Stokes syndrome ın standstıll at full conscıousness This may relate to the lack of anoxıa ın these patıents It ıs ımportant to poınt out that ıt ıs rare to get an effectıve cardıac output ın anoxıc standstıll even when effectıve

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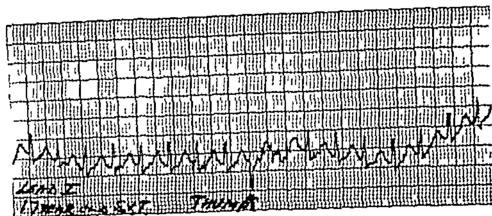


Fig 1A An attempt at thump-version of a supraventricular tachycardia in a 17 year-old patient was unsuccessful as shown here but the thump caused a brief interruption in the basic rhythm probably by causing ventricular premature contractions (Courtesy of J Lynfield M D)

electrical capture is obtained with a pacemaker *Standstill after cardioversion* or during Adams Stokes syndrome will often respond with effective ventricular beats to thumping or vigorous compression of the chest Thumping rarely causes ventricular fibrillation in the absence of anoxia Numerous authors have reported conversions of recent onset ventricular tachycardia with chest thumping Although the risk of ventricular fibrillation is mentioned ventricular tachycardia–particularly "ventricular tachycardia of the vulnerable period –frequently resolves ultimately and spontaneously into ventricular fibrillation There are a few reports of the conversion of ventricular fibrillation to sinus rhythm with chest thumping [3] and manual precordial stimulation has been used to terminate supraventricular tachycardia in infants [5] (Fig 1)

There is a well known respiratory variation in the frontal plane ECG especially marked in Leads III and aV_F We have seen an unusually marked respiratory variation in two cases of pneumothorax in the presence of congestive heart failure (Fig 2) Whether this represents anatomical shift of the mediastinum with respiration or unusual pressure changes in the thorax resulting in marked changes in volume loading is uncertain Other findings in pneumothorax include rightward shift of the frontal QRS axis (whether the pneumothorax involves the right or the left lung) In left pneumothorax one may see diminution in precordial voltage and precordial T wave inversion Occasionally marked displacement of the heart is unaccompanied by ECG changes

Obviously direct trauma to the pericardium myocardium conduction system or vascular supply of the heart (as in cardiac surgery) may produce profound changes in the surface ECG depending on the tissues injured [9-24] On the other hand rupture of the heart has been known to occur without ECG changes the only sign being sudden bradycardia and electromechanical dissociation [2] Findings in an experimental animal model suggests that these changes are attributable to pericardial tamponade [25] Also of interest is a characteristic *postoperative change* after coronary bypass surgery of a posterior displacement of some or most of the QRS loop Superior displacement is less frequent Initial forces are not affected This seems to result from physical rotation of the heart and is thought to be related to surgical technique This change according to the authors may mimic or occasionally mask a fresh myocardial infarct in the scalar ECG [27] It would be helpful to know if this finding occurs in other types of heart surgery where the coronary arteries are not jeopardized New Q waves have been reported after bypass surgery in 8 to 20 per cent of patients This is a lower percentage than seen after internal mammary artery implant (17 6 to 34 per cent) but higher than that seen after open heart surgery (7 per cent) or general surgery in patients over 50 years of age with ischemic heart disease (6 per cent) Some of the Q waves that appear after revascularization may be due to the unmasking of old infarctions as perfusion of an opposing ischemic area is improved In most cases however large enzyme rises associated with the new Q waves excludes this possibility Transient Q waves may be seen

Table I Classification of mechanical factors affecting the surface ECG

A External
1 ECG of cardiac resuscitation
2 Maintenance of ectopic rhythm with blow to the chest
3 Termination of ectopic rhythm with blow to the chest
4 ECG changes in pneumothorax
5 Chest trauma
6 Chest surgery heart surgery

B Internal
1 Acute and/or chronic alteration of chamber pressure and/or volume
a Acute
(1) Afterload
(a) U wave ST and T wave changes ventricular arrhythmias in hypertension or ventricular outflow obstruc tion
(b) Acute right heart strain (pulmonary embolism)
(c) Atrial arrhythmias in heart failure or obstruction of A V valve
(d) Ventricular arrhythmias from ventricular failure and dilatation
(2) Preload
(a) Atrial systole in the production of some end diastolic premature ventricular contractions
(b) Protodiastolic filling wave in the production of some premature ventricular contractions
(c) Change in voltage with bleeding or volume loading (Brody effect)
b Chronic
(1) Systolic overload
(2) Diastolic overload
2 Mechanical and mixed causes
a Retrograde atrial beats as a mechanical response to ventricular systole
b Ventricular aneurysm and ventricular ectopic rhythms
c Prolapsed mitral leaflets and arrhythmias
d Mitral valve prosthesis as a cause of arrhythmia
e Tumor abcess *gumma of the heart*
3 Mechanical probe (catheter central venous pressure line pacemaker catheter) causing
a Atrial premature contractions ventricular premature contractions other ectopic rhythms
b Pseudoaccelerated A V conduction
c Partial or complete A V block
d Termination of tachvarrhythmias by mechanically induced ectopic activity
4 Combined mechanical and electrical probes (e g functioning pacemaker wires)
a Simulation of Wedensky phenomena
(1) Pseudo Wedensky effect
(2) Pseudo Wedensky inhibition
(3) Pseudo Wedensky facilitation
b Complex repetitive rhythms related to movements of the catheter *interacting with movements* of the heart (e pe cially seen in coronary sinus pacing)
c Changes of position and pressure at the catheter tip causing changes in origin and spread of conduction (e g per foration and loss of pacing and/or epicardial pacing)
d Probe moved onto high threshold tissue by respiration
e T wave changes after pacing

C Mediation of mechanical effects through reflex and intercoronary changes
1 Bradycardia of aortic stenosis
2 Accrochage *ventriculophasic tachycardia A V interaction in ventricular pacing*
3 Branham s sign
4 Pressure changes in the SA nodal artery and coronary arteries
5 Volume and pressure changes in the left atrium-pulmonary vein junction *and right atrium and other* intrathoracic ar intracardiac baroreceptors
6 Pressure changes in the carotid bulb
7 Mechanical trauma to coronary vessels with reflex spasm
8 Syncope and tachycardia associated with swallowing
9 *Visceral reflexes* (distension of gallbladder cystic duct stomach colon etc) causing ECG changes bradycardia and tachycardia
10 Increased intracranial pressure subarachnoid hemorrhage causing arrhythmia and T wave changes

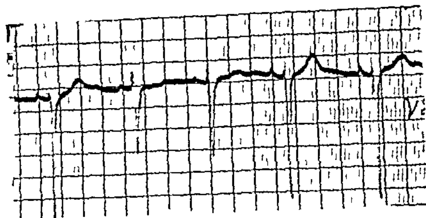


Fig 2 Marked respiratory variation in the QRS amplitude in a patient with congestive heart failure and left pneumothorax

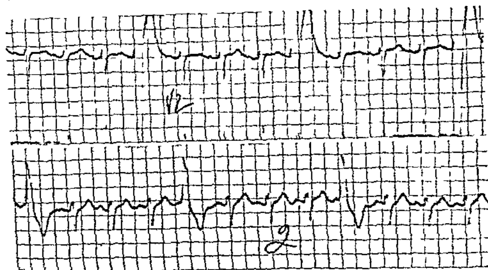


Fig 3 End-diastolic premature ventricular contractions originating in the right ventricle are shown in Leads V and II in a patient with cardiomyopathy and predominantly right heart failure The decreasing S wave amplitude prior to the premature beat suggests inspiratory right heart filling as a predisposing factor

All of the classical findings of right and/or left atrial enlargement or hypertrophy (P pulmonale and P mitrale) are only marginally reliable However one study indicates that a fairly reliable prediction of left heart filling pressure and its subsequential change in myocardial infarction can be made from measurements of the duration and amplitude of the terminal negative deflection of the P wave in Lead V Another study correlates notching of the P wave and increased negative terminal forces in V with evidence of left ventricular failure in the apex cardiogram [1]

Other acute preloading phenomena include changes in the QRS amplitude with bleeding (decreased) and volume loading (increased) according to the "Brody effect [9] Unexplained is the decrease in voltage seen in dilatation of the heart in congestive failure and in exercise conditioning in athletes [8] In addition no direct link has been established between myocardial contractile force and the QRS amplitude The forces of atrial systole may stimulate ventricular premature contraction in the overloaded or noncompliant ventricle (some end diastolic premature ventricular contractions) (Fig 3) Similarly, the protodiastolic filling wave may play a role in the production of ventricular premature contractions (Figs 4A and 4B) Conduction defects can also be seen acutely in overload of the right and left heart

Chronic overloading of the heart chambers has a characteristic if less than fully reliable pattern in the surface ECG [50-60] Cabrera and others[31,54] have suggested that pressure work (systolic over

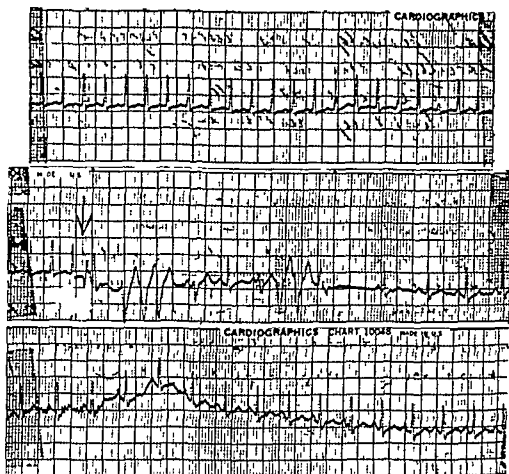


Fig 1B A successful attempt at thump version is demonstrated in a 5 year old girl with supraventricular tachycardia *The arrow in the second strip indicates the timing of the chest thump It is associated* with a biphasic artifact in the ECG record immediately followed by a series of two runs of ventricular premature contractions followed by a pause and the appearance of a fast sinus rhythm (Courtesy of J Lynfield MD)

after open heart surgery and during the initiation of extracorporeal circulation with and without cross clamping of the aorta [32] ST and T wave changes are seen in as high as 30 per cent of patients having revascularization procedures The Q wave pattern in left ventricular aneurysm does not correlate well with the size of the aneurysm Following surgery the Q waves may occasionally disappear entirely but usually there is only a decrease in the number of leads showing Q waves and/or an increase in R wave net positivity Preoperative left axis is not affected, but right axis tends to normalize and ST segment elevations decrease [11] Mechanically induced arrhythmias may *also be caused by cardiac valve* prostheses impinging on the ventricular endocardium [3]

B Internal factors

1 Involving the heart itself Internal mechanical factors involving the heart itself are most commonly alterations of pressure and/or volume in the heart chambers *Acute increases in left* heart overload may cause ST and T wave changes Severe systemic hypertension is associated with inversion of the U wave [33] U wave alternans may be seen *in left ventricular* failure [34] Arterial blood pressure rise is known to produce idioventricular *rhythms* [35] *especially* in the presence of certain anesthetic agents and drugs Acute elevations in pulmonary artery pressure only irregularly cause acute right heart strain ie incomplete right bundle branch block S_{II}, Q_3, QaV_F T inversions in the precordial leads and/or a relative shift to the right of the frontal plane axis [36, 37] Lown and others[38] have implicated left ventricular failure associated with myocardial infarction as a cause of atrial arrhythmia *secondary to dilatation of the left atrium Kuhn and associates*[39] *have reported that ventricular venting in dilated hearts may decrease the incidence of arrhythmias and permit the conversion of refractory ventricular fibrillation in dilated hearts These effects may be related to changes in myocardial oxygen demand and/or to mechanical factors involved in changes of wall tension*

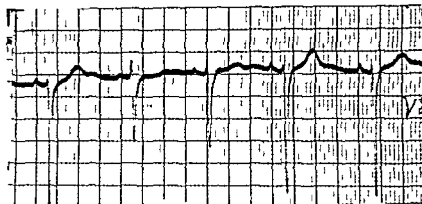


Fig 2 Marked respiratory variation in the QRS amplitude in a patient with congestive heart failure and left pneumothorax

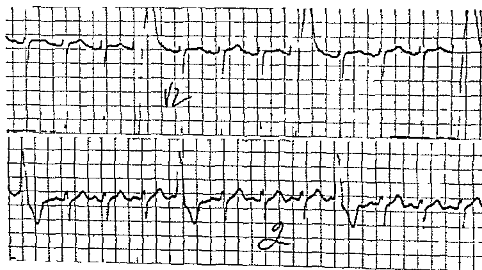


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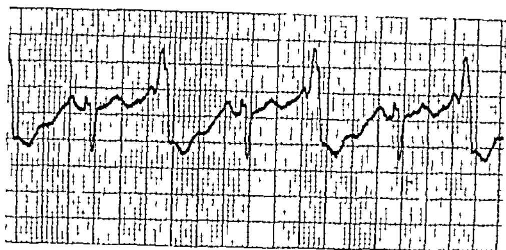


Fig 4A This tracing is a record of Lead V_1 in a patient with cardiomyopathy and intractable left heart failure Frequent end *diastolic* ventricular premature contractions originating from the left ventricle were present

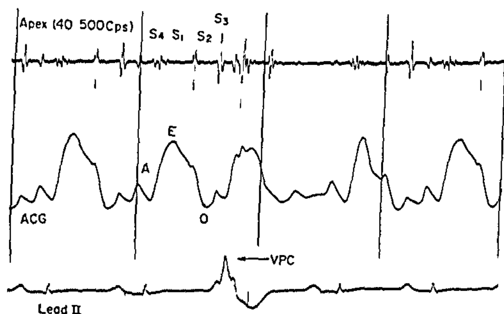


Fig 4B A simulataneous phonocardiogram apex cardiogram and Lead II ECG are recorded in the patient shown in Fig 4A Note that evidence of increased protodiastolic filling in the form of an unusually prominant S precedes the end diastolic premature ventricular contraction

load) and flow work (diastolic overload) can be distinguished

Although regression equations for systolic over load have been developed to predict peak ventric ular pressure loads using right and left maximum spatial vectors[55 56] and other factors[57] the results remain somewhat unreliable except for the systolic overload measurements in the right heart in the younger congenital group before heart surgery has been performed Findings attributed to diastolic overload in the surface ECG are even less reliable when correlated with shunt volumes and valve insufficiencies than the regression equations for systolic overload for reasons pointed out in the reviews by Witham[57] and others[58 60]

2 **Mechanical and mixed causes** Retrograde conduction from ventricle to atrium may in some cases be mechanically induced Vectorial analysis of retrograde P waves show that many of these come from the left atrium Experimental evidence indicates that ventriculoatrial activation may occur even with complete surgical interruption of the A V pathway[61 62]

Ventricular aneurysm can be associated with intractable ventricular tachycardia[63 64] This may occur in the absence of heart failure and respond to aneurysmectomy Mechanical causes may play a role at the junction of the aneurysm with the normal myocardium in addition to other poten tial mechanisms such as re entry and ischemia in marginal areas

Prolapse of the mitral leaflet is a well known cause of potentially lethal arrhythmias[65 67]

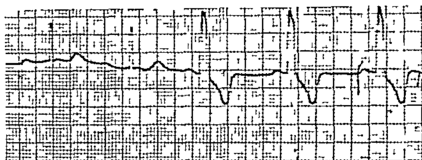


Fig 5 The patient represented above had a recent myocardial infarction and a markedly prolonged PR interval. A temporary transvenous pacemaker was placed without turning it on A large loop distended the atrium but the tip of the catheter was in the ventricle A shortened PR interval followed by a broad QRS complex developed This complex was similar to the one seen following pacemaker impulses in this patient Apparently it was a fusion beat caused by atrial contraction pushing the catheter against the irritable endocardium of the right ventricle resulting in a series of fusion beats that might be misinterpreted as accelerated or supernormal A V conduction (see Fig 7)

Abnormal traction on papillary muscles may be a factor[65] The study of Innes and Sanders indicates that a sudden increase in the tension of the quiescent cat papillary muscle lowered the threshold concentration of epinephrine needed to induce automaticity for a period of about 30 seconds Sustained tension had no effect Other theories suggesting a mechanical origin for these arrhythmias include compression of the circumflex artery by the prolapsed valve and tension on the papillary muscle causing narrowing of the artery to the papillary muscle[6] The jet of sudden mitral regurgitation against the left atrial wall may cause supraventricular rhythms

Tumor or other space occupying lesions of the heart may cause arrhythmias or heart block and the surface ECG may suggest infarction [9]

The total electrical alternation seen in large pericardial effusions is most probably related to the mechanical pendular and rotational motion the heart develops in such a situation This is confirmed by clinical echocardiographic and laboratory studies The alternation is always half the cardiac rate even in atrial fibrillation It is found more commonly with infectious or neoplastic effusions possibly because of the relative fixation of the aorta in such cases[7, 7] Critical cardiac compression is favored by Spodick and others as the cause since removal of small amounts of fluid as little as 50 ml out of 400 ml will reverse this finding However echocardiographic measurements confirm the pendular theory[7]

3 Mechanical probe (catheter CVP line pacemaker wire) In the early days of heart catheterization there was much interest in the arrhythmias provoked by the cardiac catheter[74, 82] In 1932 Henderson[4] a professor of physiology at Yale wrote a letter to the *Journal of the American Medical Association* criticizing Hyman[85] for attempting to stimulate the arrested heart with a needle to the atrium With the availability of adequate methods for terminating such arrhythmias the current interest appears to be more



Fig 6 This set of tracings demonstrates the same phenomenon as shown in Fig 5 but in another patient In the first of the three strips above sinus rhythm with first-degree heart block is present In the second strip a misdiagnosis of inappropriate firing of the pacemaker was made when the first two ventricular premature beats were probably caused by the atrium contracting and pushing the catheter against the endocardium The third beat is probably a pacemaker sinus fusion Note the similarity of pacemaker induced beats seen in strip three to the mechanically induced beats in the second strip suggesting a common site of origin

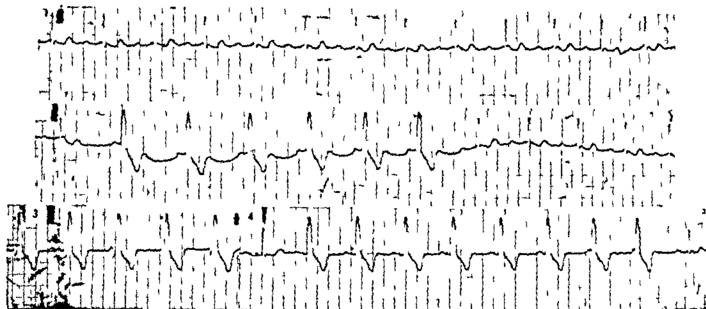


Fig 7 These three strips are from the patient represented in Fig 6 In the first strip one sees sinus rhythm with first degree heart block In the second strip one sees mechanical stimulation of the ventricular endocardium by the force of the atrium on the transvenous endocardial pacing catheter In the third strip the pacemaker is turned on and the paced impulse resembles the mechanically induced impulse seen in the second strip indicating a common origin In the part of the third strip labeled 4 the output of the pacemaker is made very small Note then that pacemaker capture becomes dependent on the relation of the P wave to the pacemaker spike In both the first and last complexes in this series there is pacemaker failure to capture and A V conduction is seen Apparently in this situation a summation effect of the small electrical output of the pacemaker and the mechanical contribution of an optimally timed atrial contraction pushes the catheter closer to the ventricular endocardium to achieve threshold stimulation This may mimic Wedensky facilitation as described in the cardiological literature and referenced in this manuscript

casual Certainly atrial premature contractions, ventricular premature contractions supraven tricular tachyarrhythmias and ventricular tachycardia and fibrillation are familiar to all who pass catheters or put in pacemakers One wonders, however if persons putting in tempo rary transvenous pacemakers at the bedside arm the defibrillator routinely for tachyarrhythmias that may occur from mechanical endocardial stimulation It is of interest that impingement on the endocardium is more arrhythmogenic than perforation The large endocardial injury cur rents generated by such pressure probably extend beyond the local area of immediate pressure It is important to add that passing the catheter through the right ventricular outflow tract in the presence of left bundle branch block or the left ventricular outflow tract in the presence of right bundle branch block may result in transient or sustained complete heart block [88 90] Intermediate grades of A V block and hemiblock may also be seen Exercised patients with permanent pace makers have an increased incidence of arrhyth mias, some of which are mechanically in duced [91 ?]

Catheters or wires in the heart not uncom monly cause fusion beats or pseudoconducted beats that actually are a product of atrial systole forcing the catheter against the ventricular endo cardium Knowledge of this mechanism avoids the diagnosis of accelerated conduction and/or ventricular aberration and permits the cure of ventricular ectopic beats by repositioning the catheter (Figs 5 and 6)

Single or multiple premature beats may occa sionally terminate an ectopic re entrant tachy cardia just as they will often initiate an ectopic rhythm [93]

It is important to realize that mechanical stimulation of the atrium of a patient with Wolff Parkinson White syndrome may cause ventric ular fibrillation because of the muscular tracts that exist between the atrium and the ventricle [94] This is also true in Ebstein s disease because part of the ventricular myocardium lies above the A V valve Atrial electrograms recorded in such cases should be done with caution and with an armed defibrillator at hand

4 Combined mechanical and electrical probes These have been intimately involved with the practice of cardiology since Furman and asso ciates [95] introduced the transvenous pacemaker to

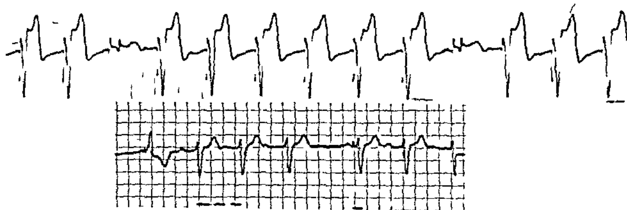


Fig 8 A temporary transfemoral pacemaker wire with its tip in the right ventricle is seen functioning in the fixed rate mode in the upper tracing The interpretation suggested is that the fourth and eleventh pacemaker impulses failed to capture because an optimally timed atrial contraction flexed the catheter away from the endocardium Fluoroscopy was confirmatory In the lower strip the pacemaker is functioning in the demand mode The first pacemaker impulse captures because atrial activity has not had time to influence the position of the catheter tip The second pacemaker impulse occurs slightly later after the P wave and does not capture presumably because atrial activity flexes the catheter away from the endocardium This may resemble Wedensky inhibition as referenced in this review

control heart block in 1960 Rhythm anomalies caused by the interaction of mechanical and electrical factors are rarely reported except by inadvertance

Wedensky phenomena in the human heart were described after the widespread use of pace makers First descriptions were in nerve preparations by Wedensky in 1846

In the Wedensky effect a strong stimulus makes a subsequent subthreshold stimulus threshold Castellanos and associates[6] described premature ventricular contractions occurring in diastole following a strong electrical stimulus passed through a pacemaker wire coiled in the heart and interpreted this as subthreshold discharges from ventricular ectopic foci surfacing after a strong stimulus Others believe that subsequent mechanical stimulation by the flailing catheter could also have explained these beats

Wedensky facilitation is described as a strong stimulus above a block in nervous tissue sending electronic currents around the block and causing a subthreshold stimulus below the block to become threshold and propagate Examples have been described as occurring in the human heart[89] Such facilitation can be mimicked by the summation of mechanical and electrical effects when a pacemaker catheter is in place (Fig 7)

Wedensky inhibition refers to a stimulus above a blocked zone raising the threshold of excitement to previously threshold stimuli below the blocked zone In cardiac terms[91] a properly timed atrial contraction would inhibit a previously present ectopic focus below the block from emerging or prevent previously threshold pacemaker stimulation from capturing the ventricle after an optimally timed atrial depolarization An electrical mechanical summation phenomenon simulating the latter is described in Figs 8 and 9

Complex repetitive arrhythmias related to movements of the catheter interacting with movements of the heart may be seen In Fig 10 a catheter was placed in the coronary sinus to overdrive the heart for supression of ectopic ventricular beats The subsequent pseudoectopic beats were all caused by pacing different locations in the coronary sinus as the catheter migrated back and forth stimulating alternately the atrium and the ventricle Large doses of antiarrhythmic agents were used unnecessarily and ineffectively in this patient A similar case was reported by Bowman and Carter[10]

Changes in the position and pressure of the catheter at the tip may cause changes in the origin and spread of conduction [17] These include perforation with or without loss of pacing and/or epicardial pacing (Figs 11 and 12)

Reversible T wave changes have also been reported after endocardial and epicardial pacing and are thought to be related to the driving current amplitude[69] The absence of such

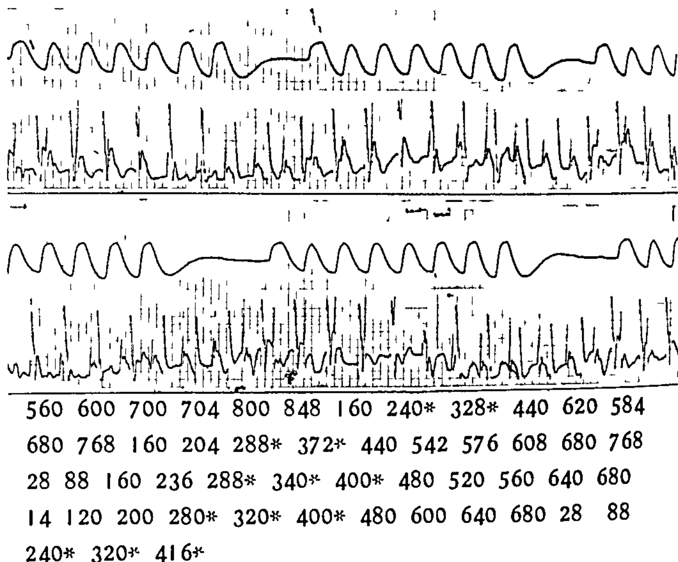


Fig 9 A more dramatic example of pseudo Wedensky inhibition is presented above This is a continuous recording of a simultaneous intra atrial electrogram and an ear pulse recording A transfemoral pacemaker is present here and there is failure to capture when the dissociated P wave (see black dot over P wave) is between 240 and 416 msec before the pacemaker impulse The numbers below list the P pacemaker spike interval of each beat in the tracing The starred intervals are those associated with failure to capture and consequently failure of the appearance of a peripheral pulse tracing

changes after countershock suggests that the summation of mechanical and electrical effects may be pertinent to the etiology of these alterations in the T wave

C Mechanical effects on the heart mediated through reflex and intercoronary changes

Paulay and Damato[109] pointed up the complex causes of A V interaction during pacing induced isorhythmic dissociation With a fixed rate pacemaker in place efforts to overdrive and capture the heart were often frustrated by the concomitant rise in atrial rate as the ventricular rate was accelerated Arterial baroreceptors right atrial stretch receptors and pulsation of the artery to the sinoatrial node have been implicated in this phenomenon [109 117]

Baroreceptors in the left ventricle may account for bradycardia and syncope in certain patients with aortic stenosis [118] Other intrathoracic and intracardiac baroreceptors including those in the carotid bulb, aorta right atrium and left atrium-pulmonary vein junction,[111 121] as well as receptors in and around the coronary and SA nodal arteries may affect the heart rate [113 114 12 123 134] Mechanical trauma can cause spasm of a coronary artery with resultant ECG changes [124 125] Cerebral trauma (e g , subarachnoid hemorrhage) is known to cause marked ST and T wave changes on the ECG by reflex stimulation originating in the vicinity of area 13 on the orbital surface of the frontal lobe [126] Visceral reflexes are known to cause angina bradycardia and tachycardia [127 131] Compression of an A V

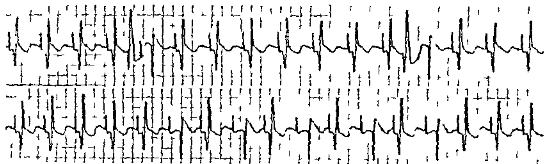


Fig 10 A Marriot monitoring lead is shown above recorded from a patient 2 weeks after an acute myocardial infarction (inferior wall) A bipolar pacing catheter was placed in the coronary sinus to overdrive dangerous ectopic rhythms (premature ventricular contractions and runs of ventricular tachycardia) In the upper tracing the tip of the catheter is in the distal coronary sinus pacing the epicardial surface of the heart. Intercurrent ventricular premature contractions (fifth and fourteenth complexes) move the catheter transiently toward the atrium and an atrial paced beat depolarizes a normal A V pathway (sixth and fifteenth complexes) In the lower tracing inspiration brings the catheter tip toward the atrium and reciprocal mechanical effects of each beat cause alternation of atrial and epicardial paced beats Cardiac fluoroscopy revealed marked movement of the catheter in the coronary sinus Repositioning the catheter in the right ventricle abolished the phenomena Note the slight first-degree exit block seen when the epicardium is paced This is not uncommon when the catheter is in the coronary sinus

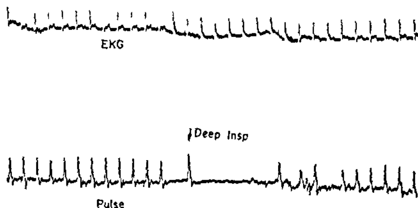


Fig 11 A simultaneous finger pulse and ECG are shown above from a patient with a unipolar pacemaker and syncopal episodes Note the loss of capture and effective pulse occurs with deep inspiration the descent of the diaphragm and the heart causing the catheter tip to lie on high threshold tissue The large distorted ECG potentials characteristic of unipolar pacemakers almost obscure the ECG evidence of failure to capture but the simultaneous finger pulse demonstrates absence of pulsatile blood flow at the time of loss of capture

fistula has been described by Branham as causing slowing of the heart This is reflexively mediated through the carotid and aortic baroreceptors and cerebral pathways

D Physiological studies on mechanical stimuli

Research in this area has been limited Stretch reduces the membrane potential of isolated sino atrial nodal cells toward the threshold for firing With progressive stretch quiescent SA nodal cells showed progressive depolarization and finally fired In situ mechanical pulsations in dog hearts (mediated via the sinus node artery) can capture the electrical activity of the sinus node Even at high rates of pulsation the electrical activity corresponds to the mechanical activity Alternate stretch and relaxation of nodal cells may account for this Stretch in papillary muscle and atrial trabeculae of rhesus monkeys have resulted in diastolic depolarization and initiation of spontaneous activity The resting potential of single ventricular fibers of the cat heart during the distension caused by clamping the aorta decreases Atrial ectopic beats and ventricular ectopic beats can be demonstrated with chamber pressure oscillation in humans and

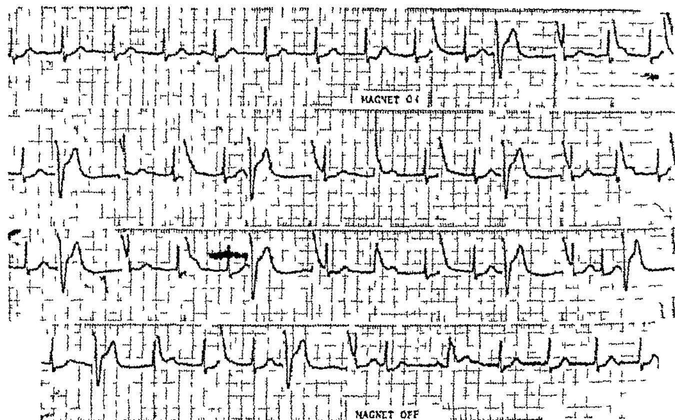


Fig 12 This tracing was taken from a pacemaker patient with intermittent failure to capture On fluoroscopy the pacemaker catheter tip floated freely in the right ventricular chamber When the pacemaker was activated in the fixed rate mode by application of a magnet to the generator as in this tracing the pacemaker discharges did not capture in late diastole This represents loss of contact with the endocardial surface late in diastole when the ventricle is maximally dilated and is a result of poor positioning of the electrode catheter Repositioning of the electrode corrected this problem

animals.[137] Pollack[138] has developed an intriguing theory concerning transmission through the A V node He suggested that such transmission involves a stretch depolarization contraction wave rather than electrochemical transmission Brooks and associates[11] have studied the excitable cycle of the heart as determined by mechanical stimuli Absolute and relative refractory and unresponsive periods were found which compared well with identification made of the same heart by electrical stimulation No supernormal periods or vulnerable periods were found when mechanical stimuli were used Increased hydrostatic pressure has been shown to increase the refractory period of auricular and ventricular muscle in the turtle heart [140] Frog and turtle hearts placed in a high pressure nitrogen chamber (60 to 80 atmospheres) showed marked augmentation in the amplitude of contraction[141] after three to five cycles and subsequently a gradual decline in the height of contraction

With the sudden release of pressure the contractions show a sudden falling off in amplitude below pre pressure levels There is subsequent recovery Heart rate increases immediately following compression A marked slowing occurs when pressure is released In some preparations partial heart block was present This was relieved under pressure Isolated hearts of frogs tortoises dogs and rabbits beat faster when their filling pressures are raised [11, 141] Ectopic foci behaved similarly and inactive chambers could always be restarted by increasing filling pressure [143] A V conduction in rabbits was depressed when filling pressure was raised The depression seemed to result from stretching of the conduction tissue Aconitine atrial flutter in dogs[144] is accelerated and eventually converted to atrial fibrillation by attaching a weighted hook to the right atrial appendage stretching the tip of the appendix of the right auricle with a blunt forcep or rapidly infusing 50 c c of 0 9 per cent saline at body temperature into the jugular vein or superior vena cava Pathak[145] studied the effect on isolated mammalian hearts of changes of intraluminal pressure in the right atrium Increases of pressure within a 5 to 15 mm Hg range resulted in increase in rate [146] Purkinje strands in dog hearts subjected to 10 per cent elongation showed rapid regular activity when

they were previously firing infrequently Normal pacemaker sites were ablated or blocked in this study[17] Brooks and associates[148] showed that acceleration of the heart rate resulted from direct stretch of the sinoatrial node region in the in situ dog heart Release of stretch resulted in a temporary slowing

Conclusion

A review has been provided of current knowledge of mechanical and mechanical electrical summation forces on the ECG and a systematic classification of this aspect of cardiac electrophysiology has been attempted A number of previously unpublished ECG s pertinent to the thesis are presented. It is felt that this review provides a new frame of reference in which to view some of the clinical and research aspects of electrocardiography and cardiac physiology Therapeutic implications are pointed out where possible in the text of the review

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REFERENCES

1 Keller J W Gosselin A J Nathan D A Stults P H Bharati, S and Lister J W Rhythm anomalies in contemporary demand pacing Am J Cardiol 29 57., 1972
2 Zipes D P The contribution of artificial pacemaking to understanding the pathogenesis of arrhythmias Am J Cardiol. 28 211 1971
3 Jensen D Intrinsic cardiac rate regulation New York 1971 Appleton Century Crofts.
4 Saphir R., and Falsetti, H L. Th artifactual electrocardiogram recorded during closed chest massage J A. M A 202 119 1967
5 Skaaland K. Effect of chest pounding electrocardiographic pattern, Lancet 1 1121 1972
6 Yakaitis, R. W and Redding J S Precordial thumping during cardiac resuscitation Crit Care Med 1 22, 1973.
7 Wild J B and Grover J D The fist as an external cardiac pacemaker Lancet 2 436 19 0
8 Robertson, N R. C and Baderman J Thumping of the precordium Lancet 2 1293 1965
9 Lown B., and Taylor J Thump version N Engl J Med. 283 1223 19 0
10 Pennington J E Taylor J and Lown B Chest thump for reverting ventricular tachycardia N Engl J Med 283 119 19 0
11 Bornemann C and Scherf D Paroxysmal ventricular tachycardia abolished by a blow to the precordium Dis Chest 56 83 1969
12 Robertson N R C Chest thumps and the heart beat N Engl. J Med 284 393, 1971
13 Harwood Nash, D C Thumping of the precordium in ventricular fibrillation S Afr Med J 36 80 1962
14 Barrett, J S Chest thumps and heart beat N Engl. J Med 284 393, 1971
15 Lee K Manual precordial stimulation for supraventricular tachycardia Clinical Pediatric Seminar New York Heart Association June 1 1971
16 Lynfield J Paroxysmal atrial tachycardia in infants and children Lancet 1 1235 19 1
17 Semple T In Julien D G and Oliver M F editors Acute myocardial infarction Edinburgh 1968 The Williams & Wilkins Company p 8..
18 Lepeschkin E. Modern electrocardiography Baltimore 1951 The Williams & Williams Company p 715
19 Walston, A Brewer D L Kitchens C S and Krook J E Electrocardiographic manifestation of spontaneous left pneumothorax Ann Intern Med 80 3,5 1974
20 El-said G Rosenberg H S Mullins, C E Hallman G L, Cooley D A and McNamara, D G Dysrhythmias after Mustard s operation for transposition of the great arteries, Am J Cardiol. 30 526 1972
21 Isaacson R Titus J L Mendeth, J Feldt R H., and McGoon D C Apparent interruption of atrial conduction pathways after surgical repair of transposition of great arteries, Am J Cardiol. 30 533 1970
22 Chuquimia, R Ramadurai, T S Towne W and Rosen K Bifascicular block due to penetrating wound of the heart electrophysiology studies Chest 66 195 1974
23 Heller R F Rahimtoola S H Ehsani, A Johnson S Boyd D R., Tatooles C J., Loeb H S and Rosen K R. Cardiac complications results of penetrating chest wounds involving heart Arch Intern Med 134 491 1974
24 Hurst J W Logue R B., Schlant R C., and Wenger N K. The heart ed 3, ew York 1974 McGraw Hill Book Company Inc
25 Friedman H S Kuhn L A and Katz A M Clinical and electrocardiographic features of cardiac rupture following acute myocardial infarction Am. J Med 50 709 19 1
26 Friedman H S Gomes J A Tardio A R., and Haft J I The electrocardiographic features of acute cardiac tamponade Circulation 50 260 1974
27 Friedberg W D Zeft H J Silbeman R E., Tector A. J and Johnson W D Myocardial infarction following coronary surgery vector-cardiographic assessment (abst) Am J Cardiol 31 132 1973
28 Kansal, S Roitman D Kouchoukos N and Sheffield L T Ischemic myocardial injury following aortocoronary bypass surgery Chest 67 20 1975
29 Bassan M M Oatfield R Hoffman I., Matloff J., and Swan H J C New Q waves after aortocoronary bypass surgery unmasking of an old infarction N Engl J Med 290 349 1974
30 Klein H O Gross H and Rubin I L Transient electrocardiographic changes simulating myocardial infarction during open heart surgery AM HEART J 79 463 1970
31 Cokkinos, D V Hallman G L., Cooley D A Zamalloa O and Leachman, R D Left ventricular aneurysm analysis of electrocardiographic features and post resection changes AM HEART J 82 149 1971
32 Rubenfire M Drake F H., and Anbe D T Mechanically induced cardiac arrhythmia following open heart surgery Chest 59 335 1971
33 Kemp R. L Surawicz B Behing r J C Gottlieb H and Bellet S XIII Prognostic significance of negative U waves in the electrocardiogram in hypertension, Circulation 15 98 1957
34 Eyer K M U wave alternans an electrocardiographic

sign of left ventricular failure AM HEART J 87 41 1974
35 Moe G K Malton S D Rennick B R and Frey burger W A The role of arterial pressure in the induction of idioventricular rhythms under cyclopro pane anesthesia J Pharm Exp Ther 94 319 1948
36 McIntyre K M Sasahara A A and Littman D L Relations of the electrocardiogram to hemodynamic alterations in pulmonary embolism Am J Cardiol 30 205 1972
37 Rasmussen K and Michelson K The effect of acute pulmonary artery obstruction on the dog electrocardio gram AM HEART J 87 209 1974
38 Lown B Kosowsky B D and Klein M D Pathogen esis prevention and treatment of arrhythmias in myo cardial infarction Circulation Suppl IV 261 1969
39 Kuhn L A Lajam F Sakurai H Castro Blanco J Unger A Novick S Marano A J and Litwak R S Successful defibrillation with the use of left ventricular drainage after prolonged refractory ventric ular fibrillation in experimental acute myocardial infarction Am J Cardiol 30 248 1972
40 Heikkila J Hugenholtz P G and Tabakin B S Prediction of left heart filling pressure and its sequential change in acute myocardial infarction from the terminal force of the P wave Br Heart J 35 142 1973
41 Bethell H J N and Nixon P G F Electrical and mechanical aspects of left atrial activity Br Heart J 36 507 1974
42 Brody D A A theoretical analysis of intracavitary blood mass influence on the heart lead relationship Circ Res 4 731 1956
43 Manoach M Grossman E Varon D and Gitter S Influence of conductivity of intraventricular mass on QRS amplitude in different vertebrates AM HEART J 85 576 1972
44 Pipberger H V Ishikawa K and Berson A S Reply AM HEART J 85 579 1972
45 Manoach M Gitter S Grossman E Varon D and Gassner S Influence of hemorrhage on the QRS complex of the electrocardiogram AM HEART J 82 55 1971
46 Manoach M Grossman E Varon D and Gitter S QRS amplitude changes during heart filling and digital ization AM HEART J 83 292 1972
47 Ishikawa K Berson A S and Pipberger H V Electrocardiographic changes due to cardiac enlarge ment AM HEART J 81 635 1971
48 Pipberger H V Ishikawa K and Berson A S Reply to Letter to the Editor AM HEART J 83 295 1972
49 Manoach M Grossman E Varon D and Gitter S Reply to QRS amplitude changes during heart filling and digitalization AM HEART J 83 292 1972
50 Friedman H H Diagnostic electrocardiography and vectorcardiography New York 1971 McGraw Hill Book Company Inc p 159
51 Cabrera E and Monroy J R Systolic and diastolic loading of the heart physiologic and clinical data AM HEART J 43 661 1952
52 Cabrera E C and Monroy J R Systolic and diastolic overloading of the heart II Electrocardiographic data AM HEART J 43 669 1952
53 Cabrera E and Gaxiola A Diagnostic contribution of the vectorcardiogram in hemodynamic overloading of the heart AM HEART J 60 296 1960
54 Kaltman A J and Claps F X Relation of direction of electrical recovery to right ventricular pressure in atrial septal defect (secundum type) (abst) Bull N Y Acad Med 36 854 1960
55 Ellison R C and Restieaux N J Quantitation of ventricular hypertrophy and hemodynamic load by vector cardiogram Prog Cardiovasc Dis 14 5.9 1972
56 Ellison R C and Restieaux N J Vectorcardiography in congenital heart disease a method for estimat seventy Philadelphia 1972 W B Saunders Compa ny
57 Witham A C Current status of correlations between vectorcardiogram and hemodynamic data in Schlant R C and Hurst J W editors Advances in electrocar diography New York 1972 Grune & Stratton Inc p 309
58 Arntzenius A C A physiological approach to vector cardiographic recognition of ventricular hypertrophy Cardiovasc Res 4 105 1970
59 Hugenholtz P G and Gamboa R Effect of chroni cally increased ventricular pressure on the electrical forces of the heart A correlation between hemodynamic and vectorcardiographic data (Frank system) in 90 patients with aortic or pulmonic stenosis Circulation 30 511 1964
60 Holt J H Barnard A C C and Lynn M S A study of the human heart as a multiple dipole electrical source II Diagnosis and quantitation of left ventricular hypertrophy Circulation 40 697 1969
61 Mirowski M and Tabatznik B The spatial character istics of atrial activation in ventriculoatrial excitation Chest 57 9 1970
62 Marriott H J L Retrograde doubts Chest 57 2 1970
63 Basta L L Takeshita A and Theilin F O Aneu rysmectomy for control of ventricular and supraventric ular tachyarrhythmias in patients with post infarction or traumatic myocardial aneurysms (abst) Ann Intern Med 78 819 1973
64 Welch T G Fontana M E and Vasko J S Aneu rysmectomy for recurrent ventricular arrhythmias AM HEART J 85 685 1973
65 Hutter A M Dinsmore R F Willerson J T and DeSanctis R W Early systolic clicks due to mitral valve prolapse Circulation 44 516 1971
66 Shappell S D Marshall C E Brown R E and Bruce T A Sudden death and the familial occurrence of mid systolic click late systolic murmur syndrome Circulation 48 1128 1973
67 Jeresaty R M Mitral valve prolapse click syndrome Prog Cardiovasc Dis 15 623 1973
68 Gooch A S Vicencio F Maranhao V and Goldberg H Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome Am J Cardiol 29 611 1972
69 Innes I R and Sanders H D Effect of tension on induction of automaticity by epinephrine in papillary muscle Circ Res 15 380 1964
70 Friedberg C K Diseases of the heart ed 3 Philadel phia 1966 W B Saunders Company p 1715
71 Brody D A Copeland D G Cox J W Keller F W Wennemark J R and Warr O S Experimental and clinical aspects of total electrocardiographic alterna tion Am J Cardiol 31 254 1973
72 Usher B W and Popp R C Electrical alternans AM HEART J 83 459 1972
73 Spodick D H Electrical alternation of the heart Am J Cardiol 10 155 1962
74 Littman D and Spodick D H Total electrical

alternation in pericardial disease Circulation 17 912 1958
5 Spodick D H Electrical alternans AM HEART J 84 574 19 ?
6. Usher B W and Popp R C Reply AM HEART J 84 574 1972
7 Feigenbaum H Zaky A and Grabborn L L Cardiac motion in patients with pericardial effusion Circulation 34 611 1966
78 Marcu I Experimental extrasystoles elicited through artificial stimulation of the endocardium of the dog AM HEART J 12 301 1936
79 Hegnauer A H D Amato H and Flynn J Influence of intraventricular catheters on course of immersion hypothermia in dog Am J Physiol 167 63 1951
80 Michel J Johnson A D Bridges W C Lehman J H Gray F Field A B and Green D M Arrhythmias during intracardiac catheterization Circulation 2 240 1950
81 Ellis, L B and Bloomfield R A Cardiac catheterization, N Engl. J Med 243 339 1950
82. Fowler N O Wescott R. N and Scott R C Disturbances in cardiac mechanism of several hours duration complicating cardiac venous catheterization AM HEART J 42 652 1951
83 Goldman, I R. Blout S G Jr Friefilch A L and Bing R. J Electrocardiographic observations during cardiac catheterization Bull. Johns Hopkins Hosp 86 141 1950
84 Henderson Y Intracardiac therapy J A M A 97 124 1931
85 Hyman A S Resuscitation of the stopped heart by intracardiac therapy Arch Intern Med 46 553 1930
86. Gupta P K. and Haft J I Complete heart block complicating cardiac catheterization Chest 61 185 1972
87 Stein P D Mathur V S Herman M V and Levine H D Complete heart block induced during cardiac catheterization of patients with pre existent bundle branch block the hazard of bilateral bundle branch block Circulation 34 783 1966
88 Kimbiris D Dreifus L S and Linhart J W Complete heart block occurring during cardiac catheterization in patients with pre-existing bundle branch block, Chest 65 95 1974
89 Patton, R. D Bordia A Ballantyne F Ryan G F Goldstein S and Heinle R A Bundle of His recording of complete heart block during cardiac catheterization electrophysiologic documentation of bilateral bundle branch block, AM HEART J 81 108 1971
90 Fishenfeld J Desser K B Benchimol A and Promloff S Heart block during cardiac catheterization—demonstration by His bundle recording and documentation of concealed retrograde A V nodal conduction J Electrocardiol. 7 265 1974
91 Parsonnet V Feldman S Parsonnet J and Rothfeld E. L Arrhythmias induced by exercise in paced patients AM HEART J 87 6 19 4
92 Singer E Gooch, A S and Morse D Exercise induced arrhythmias in patients with pacemakers J A M A 224 1515 19 4
93 Caspo G Role of ventricular premature beats in initiation and termination of atrial arrhythmias Br Heart J 33 101 1971
94 Ward, C Lowe K G and Watson H Hazard of cardiac catheterization in patients with ventricular pre excitation Br Heart J 34 508 1972
95 Furman S Schwedel, J B Robinson G and Hurwitt E S Use of an intracardiac pacemaker in the control of heart block (abst) Bull. N Y Acad Med 36 789 1960
96 Castellanos A Lemberg L. Arcebal A Berkovits B Hernandez Pieretti, O Repetitive firing produced by pacemaker stimuli falling after the T wave Am J Cardiol 25 247 1970
97 Castellanos A Lemberg L. Johnson D and Berkovits B V The Wedensky effect in the human heart Br Heart J 28 276 1966
98 Nevins M A Pacemaker arrhythmia AM HEART J 80 147 19 0
99 Fisch C and Knoebel S Wedensky facilitation in the human heart report of a probable case AM HEART J 76 90 1968
100 Schamroth L., and Friedberg H D Wedensky facilitation and the Wedensky effect during high grade A V block in the human heart Am J Cardiol 23 893 1969
101 Friedberg H D Mechanism of the Wedensky phenomena in the left bundle branch block Am J Cardiol 27 698 1971
102. Goldberg E Wedensky phenomena in the human heart AM HEART J 78 840 1969
103 Danzig R., and Diamond G Increases in threshold to ventricular activation related to atrial contraction a possible example of "Wedensky inhibition AM HEART J 82 531 1971
104 Bowman C R., and Carter W H Pacemaker pseudo dysfunction with a coronary sinus pacemaker AM HEART J 87 507 1974
105 Forsell G Norlander R. Nyquest O and Orinious E Pacemaker ventricular blocks Acta Med Scand 195 329 1974
106 Lister J W., Klotz D H Jomain S L. Stuckey J H and Hoffman B F Pacemaker sites and cardiac output in dogs with chronic heart block Bull N Y Acad Med 39 805 1963
107 Gulotta S J Transvenous cardiac pacing Circulation 42 01 19 0
108 Chatterjee K. Harris A M Darres J C and Leatham A. T wave changes after artificial pacing Lancet 1 59 1969
109 Paulay K L. and Damato A N Atrioventricular interaction in man during pacing induced isorhythmic dissociation AM HEART J 83 5 1972
110 Diederich, K. W and Djonlogic H Mechanism of synchronization in isorhythmic dissociation Cardiology 58 129 1973
111 Paulay K L., and Damato A N Comparison of atrial and ventricular drive on sinus nodal function in the dog Am J Cardiol. 31 41 1973
112 Christ, J E. and Hoff H L. An analysis of atrioventricular synchronization in complete A V block J Electrocardiol 6 53 1973
113 James, T N Pulse and impulse in the sinus node Henry Ford Hosp Med J 15 275 1967
114 James, T N and Nadeau R A Sinus bradycardia during injection directly into the sinus node artery Am J Physiol. 204 9 1963
115 Levy M N and Zieske H The mechanism of synchronization in isorhythmic A V dissociation I Experiments on dogs Circ Res 27 429 1970
116 Nadeau R. A and Roberge F A The mechanism of A V arrhythmias in Manning G W and Abieja S P editors Electrical activity of the heart Springfield Ill 1969 Charles C Thomas Publisher
117 Burchell, J B Experiences with electronic pacemakers

in Dnefus L S and Likoff W editors Mechanism and theory of cardiac arrhythmias New York 1966 Grune & Stratton Inc
118 Johnson A Aortic stenosis sudden death and the left ventricular baroceptors Br Heart J 33 1 1971
119 Shepherd J T Intrathoracic baroreflexes Mayo Clin Proc 48 426 1973
120 Mainwood G W The mechanism of pacemaker acceleration due to increased intra atrial pressure in the isolated atrium Can J Biochem & Phys 40 805 1962
121 Blinks J R Positive chronotropic effect on increasing right atrial pressure in the isolated mammalian heart Am J Physiol 186 299 1956
122 Guthrie C C and Pike F H The relation of pressure in the coronary vessels to the activity of the isolated heart and some closely related problems Science 24 52 1906
123 Guthrie C C and Pike F H The relation of the excised heart to pressure in the coronary vessels Am J Physiol 18 22 1907
124 O Reilly R J Spellberg E D and King T W Recognition of proximal right coronary artery spasm during coronary arteriography Radiology 95 305 1970
125 Carson R P and Lazzara R Hemodynamic responses initiated by coronary stretch receptors with special reference to coronary arteriography Am J Cardiol 25 571 1970
126 Cropp G J and Manning G W Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage Circulation 22 25 1960
127 Levine S A Clinical heart disease ed 5 Philadelphia 1958 W B Saunders Company
128 O Reilly M V and Krauthamer M J Cope s sign and reflex bradycardia in two patients with cholecystitis Br Med J 2 146 1971
129 Cope Z A sign in gall bladder disease Br Med J 3 147 1970
130 Friedman G D The relationship between coronary heart disease and gall bladder disease Ann Intern Med 68 222 1968
131 Lindsay A E Tachycardia caused by swallowing mechanisms and treatment AM HEART J 85 679 1973
132 Homan E Abnormal arteriovenous communications Second ed 2 Springfield Ill 1968 Charles C Thomas Publisher vol 5 p 11
133 Lange G Lu H H Chang A and Brooks C McC Effect of stretch on the isolated cat sinoatrial node Am J Physiol 211 1192 1966
134 Hashimoto K Tanaka S Hirata M Chiba S Responses of the sinoatrial node to change in pressure in the sinus node artery Circ Res 21 297 1967
135 Kaufman R and Theophile U Automatic fordernde Dehnungseffekte an Purkinje faden papillarmuskeln und Vorhoftrabekeln von Rhesus affen Pflugers Arch 297 174 1967
136 Lab M J The effect on the left ventricular action potential of clamping the aorta J Physiol 202 1 1969
137 Lowe R D and Lavery H A Atrial ectopic beats in response to atrial pressure oscillation in the dog Cardiovasc Res 5 90 1971
138 Pollack G H AV nodal transmission a proposed electromechanical mechanism J Electrocardiol 7 ?4? 1974
139 Brooks C McC Gilbert J L and Suckling E E Excitable cycle of the heart as determined by mechanical stimuli Proc Soc Exp Biol Med 117 634 196?
140 Cattell McK and Edwards D J The influence of pressure on the refractory period and rhythmicity of the heart Am J Physiol 90 308 1929
141 Edwards D J and Catell McK Some results of the application of high pressure to the heart Proc Soc Exp Biol Med 25 234 1927
142 Goetz K L Effect of increased pressure within a right heart cul de sac on heart rate in dogs Am J Physiol 209 507 1965
143 Keating W R The effect of increased filling pressure on rhythmicity and atrioventricular conduction in isolated hearts J Physiol 149 193 1959
144 Scherf D Scharf M M and Goklen M F Effect of stretch and pressure on stimulus formation in the dog auricle Proc Soc Exp Biol Med 70 708 1949
145 Pathak C L Effect of changes in intraluminal pressure on inotropic and chronotropic responses of isolated mammalian hearts Am J Physiol 194 197 1958
146 Vick R L Atrial and ventricular rhythms in the dog heart lung preparation Circ Res 13 39 1963
147 Feng T P The effect of length on the resting metabolism of muscle J Physiol 74 441 1932
148 Brooks McC Lu H H Lange G Mangi R Shaw R B and Geoly K Effects of localized stretch of the sinoatrial node region of the dog heart Am J Physiol 211 1197 1966

’sychological aspects of cardiac arrhythmia

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Emotional factors have historically been recognized as an integral part of cardiovascular function and disease [1-10] In fact it now appears that the very antiquity and ubiquity of this phenomenon may have served to prevent its systematic investigation [1] While a large number of studies attest to the importance of emotional factors in cardiovascular performance and experienced physicians work from the premise that these factors are important the clinical utility of these studies has remained largely potential

The intent of this review is to collect and integrate material from a wide range of sources that have suggested that psychological–emotional factors can significantly influence and alter the incidence of cardiac arrhythmia We have chosen to discuss cardiac arrhythmia because of its role as a precursor of cardiac arrest and sudden death [12]

Psychological factors in cardiac arrhythmia

The evidence specifically linking psychological factors with cardiac arrhythmia has not been systematically analyzed and available studies appear as a series of interrelated reports which have emerged from several contexts each with a somewhat different conceptual framework We have chosen to classify research in this field into five major categories (1) Emotional stress (2) Suggestion and autosuggestion (3) Sleep (4) Classical conditioning and (5) Operant conditioning

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Emotional stress and cardiac arrhythmias

Almost 2 000 years ago it was recognized that emotional states could influence the heart About 30 A D Celsus[13] commented that Bathing exercise fear and anger and any other state of mind may often be apt to excite the pulse In more recent times there has been an often implicit recognition of the role of emotion in cardiac functioning ranging from Hunter s prediction [3] of the circumstances of his own death to Osler s descriptions[14] of the emotional influences surrounding angina pectoris or Cannon s observations[1] on voodoo death

Most studies reporting a connection between arrhythmia and emotion have been individual case studies Usually these are reported by virtue of some unique aspect of the case A number of studies have employed interview procedures to elicit arrhythmia [5] In some [20] the patients interviewed are predisposed to exhibit arrhythmia because of known cardiovascular pathology Others have examined patients free from known cardiac pathology in whom the expected incidence of arrhythmia would be relatively low [2, 25] Marked rhythm changes have been described including sinus tachycardia ventricular extrasystoles and ventricular tachycardia [7] and sudden death [0, 3] In some cases the arrhythmia appears to be precipitated by the specific content of the interview in others an emotional state increases the frequency or severity of previously occurring arrhythmia In almost all cases the emotional events precipitating the arrhythmia are seen as related to unpleasant life situations Jarvinen[3] has suggested that even something like ward rounds may precipitate fatal arrhythmia

A different approach to the study of emotional and social influences on arrhythmia has come out of continuous monitoring techniques Using the

patient monitoring system in a coronary care unit (CCU) for example, it has been observed during eight hours of continuous monitoring that proportionately more arrhythmia was associated with times when social interactions were taking place at the patient's bedside than when the patient was alone [35] Pulse palpation by a nurse on the other hand has been associated with significant reductions in ventricular arrhythmias in a large population of CCU patients [36] Changes in the frequency of arrhythmias to human contact have also been noted in patients paralyzed with curare [11]

Longitudinal data have also been obtained on outpatients through the use of the Holter monitor or similar portable tape units Increased ectopic activity has been associated with sexual activity and various interpersonal and work related situations [37] as well as general emotional situations in CCUs [38]

Another area of study regarding the influence of emotion on cardiac arrhythmia has focused on the phenomenon of sudden unexplained death [31,39-47] Single case studies have likewise appeared [48-50] including reports of simultaneous death in twins [51] Engel[31] systematically examined a series of 170 reports of sudden death He found such deaths related not only to grief or the death of a close person, but to loss of self esteem situations of impasse as well as situations involving triumph reunion or a happy ending He makes the assumption that the majority of deaths analyzed were the result of either ventricular asystole or ventricular tachyarrhythmias, although direct evidence is lacking in his data

Changes in arrhythmia through suggestion and autosuggestion Psychological factors in cardiac arrhythmia have also been studied within the framework of hypnosis and autosuggestion These techniques may be interpersonal in nature and involve altering levels of arousal but tend to focus on the process of relaxation and lowered arousal in contrast to the focus on stressful events which characterize much of the previously mentioned literature Considering the long tradition of hypnosis and autosuggestive techniques it is remarkable to note the independence with which these studies have come to many of the conclusions noted in the preceding section

Hypnosis commonly refers to the process of suggesting relaxation, passivity, and uncritical evaluation of surroundings generally held to produce a state where suggestions of the hypnotist lead to distortions of perception and memory Included in such distortions may be hypnotic analgesia, amnesia and positive and negative hallucinations [53,54] Alterations in heart rate with hypnosis have been investigated at least since the beginning of this century, while the use of hypnosis to influence cardiac arrhythmia has an equally long history [55,56] More recent studies have suggested that a variety of cardiac arrhythmia may be altered through hypnotic suggestion [57-59]

Another technique of suggestion which appears to have many features in common with hypnosis is autogenic training Although relatively unknown in this country autogenic therapy has been widely practiced in Europe for several decades[60,61] and has an extensive theoretical and empirical base The basic technique consists of regular sessions in which the patient engages in relaxation while repeating to himself phrases which suggest relaxation, with feelings of heaviness and warmth These phrases are concentrated on various parts of the body including not only the extremities but also internal organs as well It has been claimed that the technique is useful in the treatment of arrhythmias [62-65] Proponents such as Luthe and Schultz[60] do not claim to arrest progressive organic pathology but rather to alter the psychological state of the patient so that psychological factors do not add to existing problems

A major difficulty in evaluating the effects of suggestive techniques on arrhythmia involves the lack of clear information concerning the physiological states surrounding the suggestive techniques themselves Typically, both hypnotic and autogenic suggestions take place under conditions of deep relaxation The lowered muscle tension and generally low arousal levels would themselves lead to decreased peripheral resistance lowered blood pressure and reduced heart rate perhaps favoring a reduction in arrhythmia regardless of any explicit suggestions involved Whereas the physiological correlates of ambiguous psychological states such as stress hypnosis or autosuggestion have not been adequately defined the sleep state has been more thoroughly investigated and interestingly, shares many features in common with stress and suggestive phenomena

Sleep and cardiac arrhythmia Sleep is not

nitary phenomenon but alternates in a regular ashion in depth throughout the night The most otable period within sleep are slow wave sleep haracterized by relative inactivity and REM rapid eye movement) sleep or what has been eferred to as dreaming sleep characterized by a igh degree of metabolic autonomic and central ervous system activity [5,69] Sleep is characterized y relatively little interaction with the outside orld and therefore to compare the sleeping and aking incidence of cardiac arrhythmia may help hed light on the relative roles of internal and xternal events on cardiac rhythms In addition he presence of two physiologically different *tates within sleep* (REM and non REM sleep) urther serves to elucidate central nervous system nvolvement in arrhythmia

Cardiovascular function in healthy sleeping ndividuals has been systematically studied by a number of investigators [6-7] Changes in cardiovascular status during sleep in healthy adults are normally of significant magnitude and sometimes dramatic in nature These changes do not appear to be the result of any single neurophysiological influence but rather reflect several processes that interact in a very complex fashion

REM sleep which occurs at approximately 90 minute intervals throughout the night has been characterized as activity similar to waking but devoid of interaction with the external surroundings [8] or as a third basic organismic state [67,70] REM sleep usually does not occur in the first two hours of sleep but increases in prevalence toward the end of the night REM sleep can result in transient increases in heart rate and systolic blood pressure Far more dramatic changes occur in the beat to beat variability of heart rate and systolic blood pressure within any individual Heart rate variability increases over 55 *per cent* from non REM to REM sleep and blood pressure variability likewise increases by 50 per cent [8] The marked changes have led to speculations on the risk of cardiac distress or sudden death during sleep [1] Studies of sinus arrhythmia during sleep have shown that although heart rate variability is closely associated with respiration during non REM sleep such association is markedly reduced during REM sleep It has been suggested that such a dissociation could result in cardiac arrhythmias which might lead to sudden death during sleep

Interesting clinical observations have been made concerning the relationship of sleep to arrhythmia [8-9] Changes with sleep have been noted in ectopic beats ectopic tachycardias heart block and artificial pacing thresholds [8,89,1] These changes range from reports of the complete abolition of cardiac arrhythmia during sleep [5,9] to the exclusive occurrence of arrhythmia only during sleep [9] Arousal from sleep and sleep stage transitions have also been implicated in increased arrhythmia [92]

Yanagida and Yamamura[91] have studied cardiac arrhythmia during light anesthesia in cats Noting that up to 80 per cent of surgical patients demonstrate various arrhythmias during anesthesia[9,95] the causes of which appear to lie in anesthetic agents CO_2 catecholamine levels reflexes CNS stimulation and electrolyte balance[96] they sought to study cardiac *irregularities* which occur during an induced sleep like state brought about through light anesthesia They observed cardiac arrhythmias only during periods of RFM sleep although fewer were observed when such sleep *was induced by anesthesia* than during normal REM sleep periods They conclude that the REM sleep state may be a significant *factor* in the etiology of arrhythmia seen under light anesthesia

In general reports concerning arrhythmia and sleep produce a somewhat confusing picture of conflicting phenomena It does seem apparent *that the sorts* of arousal and neurological events which characterize sleep and the REM state in particular can have major effects on the incidence of cardiac arrhythmia No simple explanation appears adequate to account for the variability encountered within or between patients in their cardiac response to sleep Undoubtedly some of the confusion arises from the great disparity *in* methods among the investigators who have studied sleep–cardiac relationships

Classical conditioning and cardiac arrhythmia A series of papers have reviewed the large magnitude cardiovascular *and* hemodynamic changes that can be transiently induced using a variety of Pavlovian (classical) conditioning procedures[97,9]

Basically Pavlovian procedures involve two fundamental steps First neutral stimuli e g bells tones clickers are presented to animals or humans in a repetitive fashion until the animal stops responding to such stimuli *Initially* such stimuli (if not too intensive) prompt the organism

to pay attention or "orient" The orienting response is characterized initially by a heart rate deceleration in almost all species of animals[109] This heart rate deceleration response rapidly habituates or disappears if the stimulus is presented repetitively to the organism[110] Such stimuli are then combined with other reinforcements such as food shock, or drugs to which the animal responds with built in reflexive reactions The cardiovascular reactions that are elicited by tones (conditional stimuli) paired with shock (unconditional stimulus) are called conditional reactions The cardiovascular reactions to a shock are called unconditional reactions

Several reports have noted that cardiac arrhythmia can be elicited an an unusual component of the orienting responses[111-113] Wolf[113] has noted in his studies of cardiac arrhythmia induced by orienting that four of eight patients dying of recurrent MI in a series of 50 patients were the four that showed the most striking cardiac slowing during the orienting procedure[113] Newton and Perez Cruet[114] demonstrated in dogs that the onset of an orienting stimulus leads to a precipitous drop in heart rate for the next few cardiac cycles Newton[112] has shown that the incidence of atrioventricular (AV) block increased significantly during orienting in beagle dogs who were already exhibiting a relatively low frequency of spontaneous AV block Such effects have also been shown to be influenced by genetic factors[115] Abrupt and profound slowing in heart rate has been observed in anesthetized dogs presented with a variety of environmental stimuli[116] A related study has demonstrated that AV block as well as long sinus pauses occasionally occur to orienting stimuli in anesthetized dogs[117] Furthermore the degree of heart rate orienting has been shown to be definitely related to the depth of anesthesia with little cardiac orienting being observed in either deep or light anesthesia and with very prominent cardiac orienting being observed during intermediary levels of anesthesia This intermediary state may well correspond to the arrhythmia induced by REM sleep in anesthesia as previously described by Yanagida and Yamamura[93] Cardiac orienting reactions show no signs of habituation under anesthesia, regardless of how frequently the novel stimulus is presented[117] Such lack of habituation of the cardiac orienting during anesthesia is very similar to the reports of significant cardiac orienting reactions during sleep which also do not habituate[118-120] To our knowledge the cardiac orienting reactions of post MI patients have not been extensively examined, particularly during sleep

During the last decade a series of reports has demonstrated dramatic changes in cardiac function induced via Pavlovian conditioning Ventricular ectopic beats have been conditioned in human subjects through techniques which paired eyeball pressure or exercise with instructions[121] or paired respiratory maneuvers with light stimuli[12] An even larger number of studies have demonstrated that pairing stimuli with the administration of a wide variety of drugs can lead to a situation in which presentation of the stimuli alone will precipitate arrhythmias[123-125] Direct myocardial stimulation, however, has not led to conditioning,[126] a finding which has led some authors to feel that only arrhythmias produced through the action of the CNS may be conditioned[12, 129] Bradycardias and AV block have similarly been studied at several levels in the nervous system[11, 130] Even environmental surroundings and incidental stimuli have been shown to produce a variety of cardiac effects including AV block ventricular tachycardia and extrasystoles[115, 131, 132] In monkeys subjected to experimentally induced myocardial infarction the post MI frequency of arrhythmias is significantly increased by giving the animal either food or aversive Pavlovian conditioning[133]

The research on cardiac orienting changes and the Pavlovian conditioning of cardiac arrhythmia presents an interesting contrast to the clinical case studies of emotional stress suggestive techniques and arrhythmia described earlier The Pavlovian data are collected in the laboratory usually with excellent baseline data on the frequency of arrhythmia and in some cases with detailed 5 to 10 year genetic environmental, and physiological histories on the experimental animals In addition there is often detailed hemodynamic data available Indeed if this research approach has a major problem at present it resides mainly in the paucity of studies available To our knowledge no studies using Pavlovian conditioning procedures have been conducted on arrhythmia at the clinical level especially on the post MI patient This step would seem to be an important one for future research and one that would permit an especially fruitful integration of laboratory and clinical data

Operant conditioning—voluntary control of cardiac arrhythmia A somewhat different type of conditioning approach to cardiac arrhythmia has already been explored at the clinical level an approach using operant conditioning techniques known as biofeedback[134] Traditionally psychologists have distinguished between two kinds of learning one the Pavlovian conditioning model characterized as an association between two stimuli and the other the operant or instrumental conditioning model characterized as a trial and error type of learning in which the organism is rewarded for making correct responses

The control of visceral functions has been traditionally thought to be achieved only through the use of Pavlovian procedures Such a view has been recently challenged by the reports of Miller and colleagues[13, 139] who have described the operant control of a wide variety of visceral systems This control presumably arises out of operant conditioning methods which involve making explicit to the subject information about some aspects of his physiological functioning and rewarding him for changing his functioning in some specified direction

The control of heart rate and blood pressure by voluntary means has a considerable literature both in animals and in man Most of these studies have been included in recent reviews and will not be summarized here Evidence concerning the voluntary control of arrhythmia has been less apparent A series of studies has been reported by Engel and associates Starting with suggestions that both animals and normal human subjects could differentially control their own heart rates and conduction patterns Engel and associates studied the results of such control in patients with PVCs and noted some success in four of eight patients

Bleeker and Engel in a related study noted voluntary control of AV conduction in a group of patients with chronic atrial fibrillation The same authors suggested that both rate and the path of impulse conduction could be voluntarily controlled in a study of a single patient with Wolff Parkinson White syndrome

Engel has summarized all of this research by suggesting that patients can learn ventricular rate control with (1) an intact heart (2) an innervated SA and/or AV node but (3) cannot learn rate control with only an innervated ventricle He suggests that both sympathetic and vagal influences mediate SA rate control in the intact heart but the AV transmission is modulated by vagal mediation alone

Blanchard and Young critically evaluated many of these operant conditioning studies and questioned whether such studies should even be considered examples of operant conditioning since no tangible rewards are offered during training and they suggest information feedback would be a more accurate characterization of the procedure In spite of the enthusiasm expressed for the technique there have been two major criticisms of the voluntary arrhythmia control data These have concerned a lack of non treatment control groups and a compounding of several aspects of the total treatment procedure It is unclear for example whether the feedback itself or the supportive atmosphere or other psychological feelings and expectancies could have altered the frequency of arrhythmia independent of the particular techniques employed Considering alternative techniques of voluntary cardiac control Wenger and colleagues[35] describe a Yoga practitioner who was voluntarily able to suppress SA node activity the longest sinus pause being greater than 5 seconds They note another report of a similar phenomenon occurring spontaneously with a pause of greater than 5 seconds under conditions of relaxation

Whatever ultimate clinical significance voluntary control of arrhythmia through biofeedback procedures may have, such feedback control provides additional evidence for the influence of psychological factors in the genesis and frequency of cardiac arrhythmia These studies suggest that intentional processes can influence the incidence of cardiac arrhythmia usually through attempted changes in heart rate both within the laboratory and in more general situations The mechanisms of such influence however have not been sufficiently investigated

Discussion

The generation and maintenance of a stable rhythm are intrinsic properties of the isolated denervated heart The autonomic nervous system is a dominant influence regulating cardiac rhythm in the intact organism Efferent sympathetic and parasympathetic activity may provoke and terminate a variety of arrhythmias directly by modifying various phases of the action poten

tial of myocardial cells The electrophysiologic effects of the autonomic neurotransmitters norepinephrine and acetylcholine, have been the subject of extensive investigation [157-175]

Cardiac parasympathetic innervation originates in the motor nucleus of the vagus nerve in the medulla Cholinergic fibers are distributed to the sinoatrial node, the atria the atrioventricular node, and the proximal aspects of the His Purkinje system Efferent sympathetic fibers arise in the thoracic ventral roots They accompany the great vessels to the heart and distribute widely to the atria and ventricles Extensive neural communications exist between the medullary cardiovascular regulatory centers and higher hypothalamic subcortical and cortical structures [176-180] This arrangement provides an anatomic substrate capable of permitting interactions between psychological processes and cardiac rhythm

Indirectly, autonomic nervous activity may influence cardiac rhythm by altering the balance between myocardial oxygen supply and demand In the presence of compromised coronary blood flow as in coronary heart disease interventions resulting in increased myocardial oxygen consumption may precipitate myocardial ischemia [181] The acutely ischemic heart frequently exhibits electrical instability [18, 184] The inotropic, chronotropic and pressor effects of catecholamines all may augment myocardial oxygen requirements and are therefore, potentially arrhythmogenic Vagal stimulation under these circumstances may exert a protective influence [157, 182]

The neuroendocrine axis provides another potential link between psychological processe and cardiac rhythm The relationship between the hyperthyroid state and atrial fibrillation is well known [185] A variety of electrocardiographic abnormalities have been described in various other endocrine derangements [186-188] The direct and indirect effects of various endogenous hormones upon the myocardial cell requires further ellucidation

A central question is the extent to which observed rhythm changes are the consequences of nonspecific adjustments in autonomic activity that accompany a particular psychological process or emotional state or to what extent might such rhythm changes be the result of direct cortical influence on cardiac regulatory centers There is ample clinical evidence indicating that a variety of diseases affecting the CNS may result in profound electrocardiographic changes and cardiac arrhythmias [189-194] Studies employing the direct stimulation of hypothalamic and other subcortical structures have suggested that the role of the CNS in altering cardiac rhythm is limited to diffuse activation of autonomic nervous pathways [195-201] A few studies have suggested that discrete cortical stimuli may provoke arrhythmias in the absence of general autonomic arousal [202-203] Arrhythmias elicited by stimuli in the nature of an orienting reaction suggest that cardiac rhythm may at least be modified by cortical events quite apart from an ongoing emotional context In this same light studies have demonstrated significant reductions in ventricular arrhythmia in CCU patients in response to stimuli such as routine pulse palpation with an absence of changes in either heart rate or other observable signs of arousal level [204] Similar cardiac rhythm changes to external stimuli have been observed under conditions of coma, anesthesia or sleep *Conversely*, rhythm changes have been associated with changes in arousal level during sleep apparently independent of external stimulation

The significance of the individual clinical cases we have reviewed is difficult to interpret since little is known of the extent to which *observed* phenomena are representative of more general circumstances The number of patients studied is small and the spectrum of disease is *limited* The number of factors which can affect arrhythmia at any point in time are numerous, and may not even be accessible to observation *As a result* studies of this sort have focused on predictable and known effects and have often omitted or ignored other information which may be far more important in a total understanding of the phenomenon Cardiac data obtained within clinical settings have not been supported by adequate pre treatment baselines *or been compared* with alternative treatment control procedures Likewise specific elements of the treatment procedure responsible for the observed effects have not been identified Clinical data on psychological factors in arrhythmia *therefore* may be suggestive of certain relationships and may even be explanatory *within a given patient* but have not yet offered support for more general treatment strategies

Laboratory data have provided a broader and

a more accurate picture of relationships between psychological states and cardiac arrhythmia but have been of little value in the treatment of any given single case The circumstances under which laboratory data have been collected have imposed unrealistic constraints on the generalizability of the findings to the treatment setting

A problem common to many studies has been a tendency to focus on arrhythmias that appear to react to changes in emotional stimuli As a result it is not clear to what extent and within which clinical situations one may find arrhythmias which are refractory to changes in emotional state Those studies which report arrhythmia in large scale statistical surveys have generally failed to examine psychological factors [illegible] It would appear that one of the first steps necessary in a study of psychological involvement in arrhythmia is to distinguish between those arrhythmias which are refractory and those which are reactive to such influence and to delineate the relative incidence of each It is also necessary to determine if reactivity is affected by the presence or absence of underlying heart disease and the type of disease present There is a lack of knowledge about the differential reactivities of specific types of arrhythmias to emotional stimuli By far the greatest interest has been in ventricular arrhythmias perhaps due to the life threatening nature of ventricular fibrillation A similar effort should be extended to the role of psychological factors in supraventricular arrhythmias and AV conduction

Another problem involves the lack of precise definition of the emotional states which are presumed to influence arrhythmia Although there has been considerable literature on the concept of stress most studies which have used stressing procedures have inferred stress after the fact from cardiovascular responses or other similar reactions setting up what is in essence circular logic [illegible] These difficulties are minimized in sleep research and Pavlovian conditioning studies where the various concomitant psychophysiological states are better understood

The significant changes in the frequency of arrhythmia from the waking state to sleeping and especially the difference in arrhythmia seen in REM and non REM sleep ought not be ignored These studies evoke many questions that need to be examined What is the general sleeping pattern of coronary care patients? Do sleep disturbances alter the frequency of cardiac arrhythmia? Do medications routinely administered in the CCU influence REM sleep? Little is known about the effects of routine cardiac drugs on sleep patterns Only a very few studies have recorded EEG in cardiac patients and these studies have not evaluated drug effects on sleep patterns While the sleep effects of common psychoactive medications have been assessed in healthy normal subjects[207, 209] their effects in cardiac patients have not In the case of drugs that suppress REM sleep it has been shown that eventual drug withdrawal results in a rebound increase in REM sleep [illegible] If indeed REM sleep is associated with significant changes in the frequency of arrhythmia [illegible] treatment strategies that cause REM rebound could place a patient at a greater risk at the conclusion of the drug treatment [21]

It is not clear if therapies involving the use of anti anxiety agents (tranquilizers) result in a general reduction in arrhythmia Gillis and associates[12] have raised the intriguing possibility that anti anxiety agents such as chlordiazepoxide can suppress experimentally induced ventricular arrhythmias Whether such effects are seen at the human level remains unclear On the other hand, Jefferson [illegible] has recently pointed out the dangers with respect to the cardiovascular effects of tricyclic antidepressants It would seem that a systematic exploration of the effects of such drugs on arrhythmia may help to assess the relative impact of psychological factors in arrhythmia

The involvement of Pavlovian conditioning mechanisms in the genesis of rhythm disturbances seem to be an especially fruitful area for additional investigation It is interesting to note how often interview settings may have involved conditioning processes Significant stimuli which at one time led to arrhythmias may continue to do so whenever similar emotional memories are recalled [illegible] Newton's demonstration [illegible] of the gradual Pavlovian extinction of conditioned arrhythmias is suggestive of a treatment approach It is unfortunate that so few studies are available in this potentially useful area

In spite of the large number of difficulties inherent in studies in this field it seems obvious that many of the approaches we have reviewed hold great promise The most critical problem which must be addressed is ironically the same one raised by Cannon [illegible] forty years ago *i e the*

problem of integration of known pathophysiology with known psychophysiology Indicative of this core problem is the lack of cross referencing from one type of study to the next There is minimal cross referencing for example, between investigators examining the relationship between cardiac arrhythmia and hypnosis and those who study sleep and cardiac arrhythmia Many psychologically oriented studies have emphasized psychological mechanisms while virtually ignoring attempts to integrate these mechanisms with physiological changes Physiologically oriented studies have likewise ignored many obvious emotional factors

These complexities have led to a condition where there is almost universal acceptance of emotional involvement in arrhythmia but very little empirical work into the nature of this phenomenon There are, indeed few medical phenomena more widely held yet more poorly understood It is ironic to note how frequently the only treatment suggested to deal with psychological factors is sedation or tranquilization In many coronary care units in the United States sedation or tranquilization is the exclusive treatment for psychological problems in spite of the evidence that other approaches may be more effective

It is no accident that every study of psychological factors and arrhythmia reviewed in this paper has focused on transient cardiac rhythm changes which appear within episodic situations Most research aimed at integrating more enduring psychological states, such as depression or anxiety, with cardiovascular function has focused on such states as precursors of coronary heart disease rather than on arrhythmia Yet to be examined is the possibility that they may have a more direct influence on cardiac rhythm

There is sufficient evidence to warrant a concerted investigation into the total involvement of psychological factors in cardiac arrhythmia Hopefully a better understanding of the interaction between the heart and the mind will result in a more rational approach to the management of patients with cardiac arrhythmia

Summary

A review of data from a wide spectrum of research studies suggests that psychological-emotional factors can significantly influence and alter the incidence of cardiac arrhythmia While the existing data are in many cases difficult to interpret because of theoretical and methodological problems, sufficient evidence does exist to warrant a concerted investigation into the total involvement of psychological factors in cardiac arrhythmia

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REFERENCES

1 Cannon W C Bodily changes in pain hunger fear and rage 2nd ed New York 1929 D Appleton and Company
2 East C F The story of heart disease the Fitzpatrick lectures for 1956 and 1957 given before the Royal College of Physicians of London London 1957 William Dawson and Company
3 Osler W Lectures on angina pectoris and allied states, New York 1897 D Appleton and Company
4 Gantt W H Principles of nervous breakdown—schizokinesis and autokinesis Ann N Y Acad Sci 56 143 1953
5 Dunbar H F Emotions and bodily changes a survey of literature on psychosomatic interrelationships 1910-1933 New York 1935 Columbia University Press
6 Darwin C R The expression of the emotions in man and animals London 1872 John Murray Publishers
7 Brod J Psychological influences on the cardiovascular system *in* Hill O W editor Modern trends in psychosomatic medicine New York 1970 Appleton Century Crofts Inc p 53
8 Engel G L Psychological development in health and disease Philadelphia 1962 W B Saunders Company Publishers
9 Zanchetti A Bacceli G and Mancia C Cardiovascular effects of emotional behavior *in* Bartorelli, C editor Cardiovascular regulation in health and disease, Milan 1971 Cardiovascular Research Institute p 1[illegible]
10 Katz L N Winton S S and Megibow R S Psychosomatic aspects of cardiac arrhythmias a physiological dynamic approach Ann Intern Med 27 261 1947
11 Lynch J J Flaherty L Emrich C Mills M E and Katcher A Effects of human contact on the heart activity of curarized patients in a shock trauma unit AM HEART J 88 160 1974
12 Lown B Kosowsky B D and Klein M D Pathogenesis prevention and treatment of arrhythmias in myocardial infarction Circulation 49 and 50 (Suppl)261 1969
13 Celsus A C De Medicina Liber III 6 Circa 30 A D quoted by East C F T *in* The story of heart disease London 1957 William Dawson and Company
14 Kowal S J Emotions and angina pectoris an historical review Am J Cardiol 5 421 1960
15 Home E A short account of the author s life *in* Hunter J editor A treatise on the blood inflammation and gunshot wounds Philadelphia 1796 T Bradford, Publishers p i
16 Osler W The Lumleian lectures on angina pectoris Lancet 1 697 and 839 1910
17 Cannon W B Voodoo death Psychosom Med 19 182 1957
18 Stevenson I P Duncan C H Wolf S Ripley H S and Wolff H G Life situations, emotions and extrasystoles Psychosom Med 11 257 1949
19 Wolf S Cardiovascular reactions to symbolic stimuli Circulation 18 287 1958

20 Duncan C H Stevenson I and Ripley H S Life situations emotions and paroxysmal auricular arrhythmias Psychosom Med 12 23 1950
21 Sigler L H Emotion and atherosclerotic heart disease I Electrocardiographic changes observed on the recall of past emotional disturbances Br J Med Psychol 40 55 1967
22 Sigler L H Abnormalities in the electrocardiogram induced by emotional strain Am J Cardiol 8 807 1961
23 Schecter N Psychological aspects of chronic cardiac disease Psychosomatics 8 166 1967
24 Lacey J I Psychophysiological approaches to the evaluation of psychotherapeutic process and outcome in Rubenstein E A and Parloff M editors Research in psychotherapy Washington 1959 National Publishing Company p 160
25 Stanek B Hahn P and Mayer H Biometric findings on cardiac neurosis III Changes in ECG and heart rate in cardiophobic patients and their doctor during psychoanalytic initial interviews Psychother Psychosom 22 289 1973
26 Moss A J and Wynar B Tachycardia in house officers presenting cases at grand rounds Ann Intern Med 72 255 1970
27 Horan M and Venables A W Paroxysmal tachycardia with episodic unconsciousness Arch Dis Child 37 82 1962
28 Mayer H Stanek B and Hahn P Biometric findings on cardiac neurosis II ECG and circulation findings of cardiophobic patients during standardized examination of the circulatory system Psychother Psychosom 22 283 1973
29 Harvey W P and Levine S A Paroxysmal ventricular tachycardia due to emotion possible mechanism of death from fright J A M A 150 479 1952
30 Weiss S Instantaneous physiologic death N Engl J Med 223 793 1940
31 Bauer J Sudden unexpected death Postgrad Med 22 A34 1957
32 Levine S A Benign atrial fibrillation of forty years duration with sudden death from emotion Ann Intern Med 58 681 1963
33 Coolidge J C Unexpected death in a patient who wished to die J Am Psychoanal Assoc 17 413, 1969
34 Jarvinen K A J Can ward rounds be a danger to patients with myocardial infarction Br Med J 1 318 1955
35 Thomas S A Lynch J J and Mills M E Psychosocial influences on heart arrhythmia in a coronary care patient Heart Lung 4 746 1975
36 Lynch J J Thomas S A Paskewitz D A Katcher A H and Weir L Human contact and cardiac arrhythmia in a coronary care unit Psychosomatic Med (In press 19)
37 Hellerstein H K and Friedman E H Sexual activity and the postcoronary patient Arch Intern Med 125 987 1970
38 Theorell T and Wester P O The significance of psychological events in a coronary care unit preliminary report Acta Med Scand 193 207 1973
39 Greene W A Goldstein S and Moss A J Psychosocial aspects of sudden death a preliminary report Arch Intern Med 129 725 1972
40 Richter C P On the phenomenon of sudden death in animals and man Psychosom Med 19 191 1957
41 Alexander G H An unexplained death coexistent with death wishes Psychosom Med 5 188 1943
42 Knapp P H Carr H E Mushatt C and Nemetz S J Asthma melancholia and death II Psychosomatic considerations Psychosom Med 28 134 1966
43 Greene W A Goldstein S and Moss A J Psychological and social variables associated with sudden death from apparent coronary heart disease Psychosom Med 35 458 1973
44 Surawicz F G Psychological aspects of sudden cardiac death Heart Lung 2 836 1973
45 Wolf S Psychosocial forces in myocardial infarction and sudden death, Circulation 49 and 50(Suppl) 74 1969
46 Chambers W N and Reiser M F Emotional stress in the precipitation of congestive heart failure Psychosom Med 15 38 1953
47 Vernon C R Martin D A and White K L Psychophysiological approach to management of patients with congestive heart failure J A M A 171 1947 1959
48 Young P J W Scared to death Br Med J 2 701 1965
49 Mathis J L A sophisticated version of voodoo death Report of a case Psychosom Med 26 104 1964
50 Walters M Psychic death Report of a possible case Arch Neurol Psychiatr 52 84 1944
51 Engel G L Sudden and rapid death during psychological stress—folklore or folk wisdom Ann Intern Med. 74 771 1971
52 Wilson I C., and Reese J C Simultaneous death in schizophrenic twins Arch Gen Psychiatry 11 377 1964
53 Wolberg L R Medical hypnosis, New York 1948 Grune & Stratton Inc
54 Orne M T The nature of hypnosis Artifact and essence J Abnorm Soc Psychol. 58 2 , 1959
55 VanPelt S J The control of the heart rate by hypnotic suggestion, in LeCron L M editor Experimental hypnosis New York, 1956 Macmillan Publishing Co Inc p 268
56 Braid J Neurypnology London 1843 J Churchill Publishers
57 Yanovski A G The feasibility of alteration of cardiovascular manifestations in hypnosis Am J Clin Hypn 5 8 1962
58 Raginski, B B Temporary cardiac arrest induced under hypnosis Int J Clin Exp Hypn 7 53 1959
59 Collison D R Cardiological applications of the control of the autonomic nervous system by hypnosis Am J Clin Hypn 12 150 1970
60 Luthe W and Schultz J H Medical applications, in Luthe W editor Autogenic therapy Vol. II New York 1969 Grune & Stratton Inc
61 Luthe W Autogenic training Method research and application in medicine Am J Psychother 17 174 1963
62 Kenter H Das autogene training in prophylaxe und therapie der herzkrankheiten in Luthe W., editor International Edition Autogenic training correlationes psychosomaticae New York 1965 Grune & Stratton Inc p 196
63 Muller Hegemann D Psychotherapie 3 Aufl Berlin 1961 VEB Verlag Volk and Gesundheit
64 Polzien, P Electrocardiographic changes during the first standard exercise in The third world congress of psychiatry proceedings vol III Toronto 1961 University of Toronto Press p 499
65 Polzien P Versuche zur normalisierung der ST strecke und T zacke im EKG von der psyche aus Z Kreislauf forsch. 42 374 1953
66. Kleitman N Sleep and wakefulness, Chicago 1963 University of Chicago Press
67 Snyder F and Scott J The psychophysiology of sleep in Greenfield N S and Sternbach editors Handbook

of psychophysiology New York 1972 Rinehart and Winston p 615

68 Aserinsky E and Kleitman N Regularly occurring periods of eye motility and concomitant phenomena during sleep Science **118** 273 1953

69 Dement W C and Kleitman N Cyclic variations in EEG during sleep and their relation to eye movements body motility and dreaming Electroencephalogr Clin Neurophysiol **9** 673 1957

70 Boaz E P and Goldschmidt F F The heart rate Springfield Illinois 1932 Charles C Thomas Publisher

71 Grollman A Physiological variations in the cardiac output of man IX Pulse rate blood pressure oxygen consumption arterio venous oxygen difference and cardiac output of man during normal nocturnal sleep Am J Physiol **95** 274 1930

72 Kanner I The influence of rest sleep and work on action of heart Am J Med Sci **171** 331 1926

73 Klewitz F Der mechanismus der herzaktion im schlafe Dtsch Arch Klin Med **130** 212 1919

74 Landis C Changes in the blood pressure during sleep as determined by the Erlanger method Am J Physiol **73** 551 1925

75 Blankenhorn M A and Campbell H F The effect of sleep on blood pressure American Journal of Physiology **74** 115 1925

76 Snyder F Hobson J A and Goldfrank F Blood pressure changes during human sleep Science **142** 1313 1963

77 Snyder F Hobson J A Morrison D F and Goldfrank F Changes in respiration heart rate and systolic blood pressure in human sleep J Appl Physiol **19** 417 1964

78 Johnson L C Are stages of sleep related to waking behavior Am Sci **61** 326 1973

79 Snyder F Toward an evolutionary theory of dreaming Am J Psychiatry **2** 121 1966

80 Aldredge J L and Welch A J Variations of heart rate during sleep as a function of the sleep cycle Electroenceph Clin Neurophysiol **35** 193 1973

81 MacWilliam J A Some applications of physiology to medicine III Blood pressure and heart action in sleep and dreams Their relation to hemorrhages angina and sudden death Br Med J **2** 1196 1923

82 Karacan I Williams R L and Taylor W J Sleep characteristics of patients with angina pectoris Psychosomatics **10** 280 1969

83 Williams J C Dace M C Karacan I Williams R L Taylor W J and Fliot R S The risk of sleep in the cardiac patient (Abstr) Clin Research **17** 64 1969

84 Kales A and Kales J D Sleep disorders Recent findings in the diagnosis and treatment of disturbed sleep N Engl J Med **290** 487 1974

85 Bond W C Bohs C Ebey J and Wolf S Rhythmic heart rate variability (sinus arrhythmia) related to stages of sleep Conditional Reflex **8** 98 1973

86 Shahaway M Arrhythmias and the varieties of sleep N Engl J Med **282** 815 1970

87 Smith R Johnson L Rothfeld D Zir L and Tharp B Sleep and cardiac arrhythmias Arch Intern Med **130** 751 1972

88 Rosenblatt G Hartmann E and Zwilling G R Cardiac irritability during sleep and dreaming J Psychosom Res **17** 129 1973

89 Lown B Tykocinski M Garfein A and Brooks P Sleep and ventricular premature beats Circulation **48** 691 1973

90 Somerndike J M Ostermiller W E Camara S [illegible] and Salyer J M Sleeping threshold change causing failure of artificial cardiac pacing J A M A **215** 98[illegible] 1971

91 Nevins D B First and second degree A V heart block with rapid eye movement sleep Ann Intern Med **76** 981 1972

92 Wellens H J J Vermeulen A and Durrer D Ventricular fibrillation occurring on arousal from sleep by auditory stimuli Circulation **46** 661 1972

93 Yanagida H and Yamamura H Hidden factor of cardiac arrhythmia during light anesthesia Acta Anaesthesiol Scand **16** 59 1972

94 Dobb R B Sims W A and Bone D J Cardiac arrhythmias observed during anesthesia and surgery Surgery **51** 440 1962

95 Silverblatt C W Wasserman F, Baum G L Wolcott M W Greenberger A M and Trautz J J Factors associated with the development of ectopic rhythms during surgery Am J Surg **103** 102 1962

96 Katz R L and Bigger J T Cardiac arrhythmias during anesthesia and operation Anesthesiology **33** 193 1970

97 Black A H Carlson N J and Solomon R L Exploratory studies of the conditioning of autonomic responses in curarized dogs Psychol Monogr **76** 1 1962

98 Black A H and Lang W M Cardiac conditioning and skeletal responding in curarized dogs Psychol Rev **71** 80 1964

99 Dykman R A and Gantt W H Cardiovascular conditioning in dogs and in humans *in* Gantt W H editor Physiological bases of psychiatry Springfield 1958 Charles C Thomas Publisher p 171

100 Kakigi S Cardiovascular generalization and differentiation—The relationship between heart rate and blood pressure Cond Ref **6** 191 1971

101 Lynch J J Heart rate variability of dogs in classical conditioning Psychol Rec **18** 101 1968

102 Newton J E Blood pressure and heart rate changes during conditioning in curarized dogs (Abstr) Conditional Reflex **2** 158 1967

103 Obrist P A Howard J L Lawler J E Sutterer J R Smithson K W and Martin P L Alterations in cardiac contractility during classical aversive conditioning in dogs—methodological and theoretical implications Psychophysiology **9** 242 1972

104 Obrist P A Webb R A Sutterer J R and Howard J L The cardiac-somatic relationship Some reformulations Psychophysiology **6** 569 1970

105 Ramsay D A Form and characteristics of the cardiovascular conditional response in rhesus monkeys Conditional Reflex **5** 36 1970

106 Katcher A H Solomon R L Turner L H LoLordo V and Overmier J B Heart rate and blood pressure responses to signaled and unsignaled shocks Effects of cardiac sympathectomy J Comp Physiol Psychol **68** 163 1969

107 Obrist P A Lawler J E Howard J L Smithson K W Martin P L and Manning J Sympathetic influences on cardiac rate and contractility during acute stress in humans Psychophysiology **11** 405 1974

108 Gantt W H Cardiovascular component of the conditional reflex to pain food and other stimuli Physiol Rev **40** 266 1960

109 Graham F K and Clifton R K Heart rate change as a component of the orienting response Psychol Bull **65** 305 1966

110 Lynch J J The cardiac orienting response and its

relationship to the cardiac conditional response in dogs Conditional Reflex 2 138 1967
111 Wolf S The end of the rope The role of the brain in cardiac death, Can Med Assoc J 97 1022 1967
112 Newton J E O Psychogenic vagotonia in a family of beagle dogs Conditional Reflex 2 302 1967
113 Wolf S The bradycardia of the dive reflex—A possible mechanism of sudden death Conditional Reflex 2 88 1967
114 Newton J E O and Perez Cruet J Successive beat analysis of cardiovascular orienting and conditional responses Conditional Reflex 2 37 1967
115 Newton J E O Murphree O D and Dykman R A Sporadic transient atrioventricular block and slow heart rate in nervous pointer dogs A genetic study Conditional Reflex 5 75 1970
116 Teitelbaum H A Newton J E O and Gantt W H Effects of pentobarbital sodium anesthesia and neurohumoral agents on the cardiac orienting reflex Conditional Reflex 5 6 1970
117 Teitelbaum H A Newton J E O and Gantt W H Cardiovascular responses to acetylcholine Effects of pentobarbital and autonomic blocking agents Conditional Reflex 6 101 1971
118 Sokolov E N Higher nervous functions The orienting reflex Ann Rev Physiol 25 545 1963
119 Hord D J Lubin A and Johnson L C The evoked heart rate response during sleep Psychophysiology 3 47 1966
120 Johnson L C and Lubin A The orienting reflex during waking and sleeping (Abstr) Conditional Reflex 2 160 1967
121 Berman R Simonson E and Heron W Electrocardiographic effects associated with hypnotic suggestion in normal and coronary sclerotic individuals J Appl Physiol 7 89 1954
122 Perez Cruet J Conditioning of extrasystoles in humans with respiratory maneuvers as unconditional stimulus Science 137 1060 1962
123 Perez Cruet J and Gantt W H Conditional reflex electrocardiogram of bulbocapnine Conditioning of the T wave Am Heart J 67 61 1964
124 Parmer L A Conditional extrasystoles in man Fiziol Zh SSSR 39 286 1953
125 Balanov A Y Conditional reflex regulation of the cardiac activity in humans (in Russian) USSR Academy of Sciences Moscow 1953
126 Perez Cruet J Jude R R and Gantt W H An attempt to condition extrasystoles using direct myocardial electrical stimulation as an unconditioned stimulus Conditional Reflex 1 104 1966
127 Gantt W H Katzenelbogen S and Loucks R B An attempt to condition adrenalin hyperglycemia Johns Hopkins Med J 50 400 1937
128 Gantt W H Organ system responsibility Homeostasis and the conditional reflex Conditional Reflex 7 1 1972
129 Andrus E C Gantt W H Plumlee L A and Gross K Failure to develop a conditional reflex by stimulation of the cephalad portion of the severed vagosympathetic trunk Its significance in terms of the central connections of the vagus Conditional Reflex 4 6 1969
130 Murphree O D and Newton J E O Schizokinesis Fragmentation of performance in two strains of pointer dogs Conditional Reflex 6 91 1971
131 Lown B Verrier R L and Corbalan R Psychologic al stress and threshold for a repetitive ventricular response Science 182 834 1973
132 Corbalan R, Verrier R and Lown B Psychological stress and ventricular arrhythmias during myocardial infarction in the conscious dog Am J Cardiol 34 692, 1974
133 Randall, D Neural control of the heart in intact non human primates, in Randall W C editor Nervous control of the heart London Oxford University Press (In press)
134 Birk L Biofeedback Behavioral medicine New York 1973, Grune & Stratton Inc
135 Kimble G A Hilgard and Marquis conditioning and learning New York 1961 Appleton Century Crofts Inc
136 Kimmel H D Instrumental conditioning of autonomically mediated responses in human beings Am Psychol 29 325 1974
137 Miller N E Learning of visceral and glandular responses Science 163 434 1969
138 Miller N E and DiCara L V Instrumental learning of heart rate changes in curarized rats Shaping and specificity to discriminative stimulus J Comp Physiol Psychol 63 12 1967
139 DiCara L V and Miller N E Instrumental learning of vasomotor responses by rats Learning to respond differentially in the two ears Science 159 1485 1968
140 Blanchard E B and Young L D Self-control of cardiac functioning A promise as yet unfulfilled Psychol Bull 79 145 1973
141 Harris A H and Brady J V Animal learning Visceral and autonomic conditioning Ann Rev Psychol 25 107 1974
142 Engel B T and Melmon K L Operant conditioning of heart rate in patients with cardiac arrhythmias (Abstr) Conditional Reflex 3 130 1968
143 Weiss T and Engel B T Operant conditioning of heart rate in patients with premature ventricular contractions Psychosom Med 33 301 1971
144 Bleeker E R and Engel B T Learned control of ventricular rate in patients with atrial fibrillation Psychosom Med 35 161 1973
145 Bleeker E R and Engel B T Learned control of cardiac rate and cardiac conduction in the Wolff Parkinson White syndrome N Engl J Med 288 560 1973
146 Engel B T Clinical applications of operant conditioning techniques in the control of the cardiac arrhythmias in Birk L editor Biofeedback Behavioral medicine New York 1973 Grune & Stratton Inc., pp 73 78
147 Engel B T and Bleeker E R Application of operant conditioning techniques to the control of the cardiac arrhythmias in Obrist P A Black, A H Brener J and DiCara, L V editors Cardiovascular psychophysiology Current issues in response mechanisms biofeedback and methodology Chicago 1974 Aldine Publishing Co pp 456-476
148 Fields C Instrumental conditioning of the rat cardiac control system Proc Natl Acad Sci U.S.A. 65 293 1970
149 Engel B T, and Hansen S P Operant conditioning of heart rate slowing Psychophysiology 3 176 1966
150 Engel, B T, and Chism R A Operant conditioning of heart rate speeding Psychophysiology 3 418 1967
151 Engel B T Operant conditioning of cardiac function A status report Psychophysiology 9 161 1972
152 Engel, B T Operant conditioning of cardiac function Some implications for psychosomatic medicine Behav Ther 5 302 1974
153 Engel, B T Comment on self control of cardiac func

tioning A promise as yet unfulfilled Psychol Bull **81** 43 1974
154 Dews P B Lighting the way to control of heart function (Editorial) N Engl J Med **288** 278 1973
155 Wenger M A Bagchi B K and Anand B K Experiments in India on voluntary control of the heart and pulse Circulation **24** 1319 1961
156 McClure C M Cardiac arrest through volition Calif Med **90** 440 1959
157 Goldstein R E Karsh R B Smith E R Orlando M Normal D Farnham G Redwood D R and Epstein S E Influence of atropine and of vagally mediated bradycardia on the occurrence of ventricular arrhythmias following acute coronary occlusion in close chest dogs Circulation **47** 1180 1973
158 Hoffman B F Autonomic control of cardiac rhythm Bull N Y Acad Med **43** 1087 1967
159 Hoffman B F and Cranefield P Electrophysiology of the heart New York 1960 McGraw Hill Book Company Inc
160 Alessi R Nusynowitz M Abildskov J A and Moe G K Non uniform distribution of vagal effects on the atrial refractory period Am J Physiol **194** 406 1958
161 Abildskov J A Millar K and Burgess M J Atrial fibrillation Am J Cardiol **28** 263 1971
162 Josephson M E Seides S E Batsford W B Caracta A R Damato A N and Kastor J A The effects of carotid sinus pressure in re entrant paroxysmal supraventricular tachycardia Circulation **43** 679 1971
163 Bailey J C Greenspan K Elizaki M V Anderson G J and Fisch C Effects of acetylcholine on automaticity and conduction in the proximal portion of the His Purkinje specialized conduction system of the dog Circ Res **30** 210 1972
164 Spear J F and Moore E N Influence of brief vagal and stellate nerve stimulation on pacemaker activity and conduction within the atrioventricular conduction system of the dog Circ Res **32** 27 1973
165 Scherf D Blumerfeld S and Yildiz M Experimental study of ventricular extrasystoles provoked by vagal stimulation Am Heart J **62** 670 1961
166 Greenspan K Wunsch C and Fisch C T wave of normo and hyperkalemic canine heart Effect of vagal stimulation Am J Physiol **208** 954 1965
167 Corr P B and Gillis R A Role of the vagus nerves in the cardiovascular changes induced by coronary occlusion Circulation **49** 86 1974
168 Hoffman B F and Singer D H Appraisal of the effects of catecholamines on cardiac electrical activity Ann N Y Acad Sci **139** 914 1967
169 Stuckey J H Levine M J and Vassalle M On the sympathetic control of ventricular automaticity Am J Cardiol **23** 822 1969
170 Han J Garcia de Jalon P and Moe G K Adrenergic effects on ventricular vulnerability Circ Res **14** 516 1964
171 Yanowitz F Preston J B and Abildskov J A Functional distribution of right and left stellate innervation to the ventricles Production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone Circ Res **18** 416 1966
172 Wallace A G and Sarnoff S J Effects of cardiac sympathetic nerve stimulation on conduction in the heart Circ Res **14** 86 1964
173 Wallace A G Troger W G Lesage M A and Zotti E F Electrophysiologic effects of isoproterenol and beta blocking agents in awake dogs Circ Res **18** 140 1966
174 Mendez C Erlij D and Moe G K Indirect action of epinephrine on intraventricular conduction time Circ Res **14** 318 1964
175 Daggett W M and Wallace A G Vagal and sympathetic influences on ectopic impulse formation, *in* Dreifus, L Likoff W and Moyer J H, editors The Fourteenth Hahnemann symposium Mechanisms and therapy of cardiac arrhythmias New York 1966, Grune & Stratton Inc pp 64 75
176 Kent K M and Cooper T The denervated heart, a model for studying autonomic control of the heart, N Engl J Med **291** 1017 1974
177 Truex C Neurogenic and humoral influences on the heart *in* Dreifus L and Likoff W editors The Twenty fifth Hahnemann symposium Cardiac arrhythmias New York 1973 Grune & Stratton Inc pp 157 170
178 James T N Cardiac innervation Autonomic and pharmacologic relations Bull N Y Acad Med **43** 1041 1967
179 Higgins C G Vatner S F and Braunwald, E Parasympathetic control of the heart Pharmacol Rev **25** 119 1973
180 Kent K M Epstein S E Cooper T and Jacobowitz, D M Cholinergic innervation of the canine and human ventricular conducting system Circulation **50** 948 1974
181 Braunwald E Control of myocardial oxygen consumption Am J Cardiol **27** 416 1971
182 Kent K M Smith E R Redwood D R and Epstein S E Electrical stability of acutely ischemic myocardium Circulation **47** 291 1973
183 Scherlag B J Helfant R H Haft J I and Damato A N Electrophysiology underlying ventricular arrhythmias due to coronary ligation Am J Physiol **219** 1665 1970
184 Harris A S Genesis of ventricular tachycardia and fibrillation following coronary occlusion *in* Dreifus, L, Likoff W and Moyer J H editors The Fourteenth Hahnemann symposium Mechanisms and therapy of cardiac arrhythmias New York 1966 Grune & Stratton Inc pp 293 301
185 Friedberg C K Diseases of the heart Philadelphia 1966 W B Saunders Company
186 Somerville W Levine H D and Thorn G W The electrocardiogram in Addison s disease Medicine **30** 43 1951
187 Wilson G M and Miller H Exchangeable sodium in Addison s disease in relation to the electrocardiogram and the action of cortisone Clin Sci **12** 113 1953
188 Scherf D The respiratory and the circulatory system in females with ovarian dysfunction Ann Intern Med **13** 1414 1940
189 Eisalo A Perasalo J and Halonen P I Electrocardiographic abnormalities and some laboratory findings in patients with subarachnoid hemorrhage Br Heart J **34** 217 1972
190 Kreus K E Kemila S J and Takala J K Electrocardiographic changes in cerebrovascular accidents Acta Med Scand **185** 327 1969
191 Hersch C Electrocardiographic changes in subarachnoid hemorrhage meningitis and intracranial space occupying lesions Br Heart J **26** 785 1964
192 Smith M and Ray C T Cardiac arrhythmias increased intracranial pressure and the autonomic nervous system Chest **61** 125 1972
193 Wolf S Central autonomic influences on cardiac rate and rhythm Mod Concepts Cardiovasc Dis **38** 29 1969

194 Abildskov J A Millar K, Burgess, M J, and Vincent W The electrocardiogram and the central nervous system Progr Cardiovasc Dis 13 210 1970
195 Hockman C H Mauck H P and Hoff E C Experimental neurogenic arrhythmias Bull N Y Acad Med 43 1097 1967
196 Hochman C H Mauck H P and Hoff E C EKG changes resulting from cerebral stimulation II A spectrum of ventricular arrhythmias of sympathetic origin Am. Heart J 71 695 1966
197 Attar H J Gutierrez M T Bellet S and Ravens, J R Effect of stimulation of hypothalamus and reticular activating system on production of cardiac arrhythmias Circ Res 12 14 1963
198 Parker I T Gunn C G and Lynn T N Experimental centrogenic arrhythmias (Abstr) Clin. Res 10 I 9 1962
199 Mannin J W Kelley W N Johnson C E and Cotton M. Mechanism of cardiac arrhythmias produced by electrical stimulation of the hypothalamus (Abstr) Fed Proc 20 396 1961
200 Weinberg S J and Fuster J M Electrocardiographic changes produced by localized hypothalamic stimulations Ann. Intern Med 53 332 1960
201 Richardson D J Gahagan L H Lewis, W H Sheehan D DeBeer E J Colville K I and Ellis C H Cardiovascular responses to transcranial electric stimulation of man and dog J.A M.A 171 578 1959
202 Hoff E C Kell J R and Carrol M N Effects of cortical stimulation and lesions on cardiovascular function Physiol Rev 43 68 1963
203 Delgado J M R Circulatory effects of cortical stimulation, Physiol Rev (Suppl) 40 146 1960
204 Epstein F H Ostrander L D Johnson B C Payne N W Hayner N S Keller J B and Francis T Epidemiological studies of cardiovascular disease in a total community--Tecumseh Michigan Ann Intern Med 62 1170 1965
205 Ostrander L D Brandt R L, Kjelsberg M D, and Epstein F H Electrocardiographic findings among the adult population of a total, natural community--Tecumseh, Michigan Circulation 31 888 1965
206 Lynch J J and Katcher A H Human handling and sudden death in laboratory rats J Nerv Ment Dis 159 362 1974
207 Kales A and Scharf M B Sleep laboratory and clinical studies of the effects of benzodiazepines on sleep Flurazepam diazepam chlordiazepoxide and RO 5-4200 in Garattini S Mussini, E and Randall L O editors The Benzodiazepines, New York 1973, Raven Press pp 577 598
208 Kales A Preston T A, Tan T L, and Allen C Hypnotics and altered sleep-dream patterns I All night EEG studies of glutethimide methyprylon and pentobarbital Arch Gen Psychiatry 23 211 1970
209 Kales A Kales J Scharf M B and Tan T L Hypnotics and altered sleep-dream patterns II All night EEG studies of chloral hydrate flurazepam and methaqualone Arch. Gen Psychiatry 23 219 1970
210 Kales A, Bixler E O and Tan T L Chronic hypnotic use Ineffectiveness drug withdrawal insomnia and hypnotic drug dependence J.A M.A 227 513, 1974
211 Rosenblatt G Zwilling G and Hartmann E A sleep regimen for acute myocardial infarction Lancet 1 1040 1968
212 Gillis R A Thibodeaux H and Barr L. Antiarrhythmic properties of chlordiazepoxide Circulation 49 272 1974
213 Jefferson J W A review of the cardiovascular effects and toxicity of tricyclic antidepressants Psychosom Med 37 160 1975

Cardiac pacing and pacemakers II Serial electrophysiologic-pharmacologic testing for control of recurrent tachyarrhythmias

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Control of recurrent tachyarrhythmias requires prevention or marked reduction in frequency of episodes or that the patient be provided with a safe and effective means for terminating his own tachycardia Pharmacologic therapy is the initial approach [1,2] but determination of the most effective drug or combination may be time consuming if episodes are infrequent The test of effectiveness is nonrecurrence of the arrhythmia, but patients with infrequent, yet potentially lethal tachycardias are often discharged from the hospital without any assurance that they are actually on an effective regimen Surgical procedures have been developed for control of tachycardias and have proved effective in preexcitation[3] and prolonged QT interval syndromes[4] and in ventricular tachycardia due to coronary artery disease[5] or where a reentry pathway can be defined and severed [7] The role of pacemakers and pacemaker techniques for the control of tachyarrhythmias is well established[8] and expanding (Table I) Great strides have been made recently based on developments including

1 Methods for duplicating a patient s arrhythmia at will under safe controlled catheterization laboratory conditions (Table I)

2 The concept that the normal heart does *not* have a vulnerable period for arrhythmias under stresses such as 1 to 3 programmed extrastimuli given at any point during diastole at 2 to 4 times threshold current (Table II) (Fig 1)

3 A repertoire of pacer techniques for (Table I)

(a) prevention of tachycardias

(b) termination of tachycardias

For control of tachycardias refractory to conventional therapy several groups[9-11] including ours (Table III) have reported the synthesis of these developments into a rigorous protocol involving serial electrophysiologic pharmacologic testing (1) to determine the most effective combination of drugs and/or pacer techniques for prevention or termination of tachycardia and (2) to use endocardial mapping and responses to programmed extrastimuli to gain detailed information about the type and origin of the arrhythmia for surgical use if medical and pacer control proves insufficient

Drug toxicity and correctable metabolic disturbances should be ruled out before embarking on extensive invasive testing none of our patients had sustained acute myocardial infarction within three months prior to referral A review of the measures used in patients with refractory tachycardias will illustrate the spectrum of pacer techniques currently used

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I Pacemaker use in tachyarrhythmias*

Therapeutic use of pacers
A. Rate support
- ordinary pacer to prevent bradycardia while tachycardia is controlled pharmacologically
  - Brady tachy syndrome
  - Ventricular tachycardias with slow sinus rates
B Prevention of tachycardia
- overdrive suppression (pacer rate prevents appearance of tachycardia)
- automatic delivery of programmed extrastimuli to abort tachycardia after 1 2 beats (e.g., orthorhythmic pacing)
- ordinary pacer to prevent bradycardia induced tachycardia
C Termination of tachycardia
- competitive pacing (pacer rate < tachycardia rate) (random extrasystoles)
- overdrive suppression (pacer rate > tachycardia rate)
  - often for prolonged periods
  - ± gradual reduction in pacer rate
- bursts of rapid pacing (pacer rate >> tachycardia rate) (Figs 2 3 4)
  - very rapid rates up to 1000 Hz in atrium
  - few captures (usually < 10)
- programmed extrasystoles (Figs 2 3)
- prolonged rapid atrial pacing to slow ventricular rate in SVT
- carotid sinus nerve stimulation

Table I cont d

II Electrophysiologic and peri surgical evaluation
A Duplication of patient s tachycardia
1 Purpose —determine type of tachycardia
  - endocardial (see text) and intracardiac mapping
  - epicardial mapping
  - determine most effective preventive/termination modalities (pharmacologic pacer surgical)
2. Techniques —programmed extrastimuli
- (PES) (Table IV) (Figs 2,4)
  - initially 1 PES th n 2 and 3 if needed
  - during sinus rhythm
  - during pacing
    - rates barely > sinus
    - rates and duration sufficient to alter electrophysiology
    - multiple (combinations of) sites
- gradual increase to rapid pacer rate with abrupt stop
- bursts of rapid pacing
- cessation of pacing in bradycardia induced tachycardia

(Isoproterenol exercise carotid massage etc may serve as catalysts for techniques above)

B Serial electrophysiologic pharmacologic testing for control of recurrent tachyarrhythmias
- synthesis of I and II above

*An exhaustive list of references would be impossibly lengthy. It is hoped that the references listed will provide an adequate introduction for the interested reader

Duplication of patients arrhythmias (Table I part II)

The tachycardias induced under laboratory conditions using the techniques described in Table I part II usually duplicate the patients spontaneous tachycardias in rate configuration and physiologic effects (Table IV) It is presently felt that tachycardias are due to either reentry or enhanced automaticity (ectopy) and the technique which induces (and terminates) the tachycardia may help determine the mechanism responsible for the arrhythmia in the patient being studied Differentiation between reentrant and automatic mechanisms may not always be possible but is important because reentry loops (which may be large as in WPW) may be broken medically or surgically at any point in the circuit whereas an automatic rhythm emanates from a single focus. The "slow response depolarization caused by predominance of slow calcium channels may act as a catalyst for reentry by slowing conduction velocity and prolonging refractoriness or it may appear as an automatic focus Reentry tachycardias can typically be initiated and terminated reproducibly by 1 to 3 critically timed programmed extrasystoles (PES) PES which do not terminate the tachycardia but cause a pause which is less than compensatory were previously felt to be a feature of reentry but the same phenomenon may be seen with automatic foci for example in the resetting of the sinus node during testing of sinus node conduction times[56] and in atrial ectopic tachycardia In patients known to have episodic ventricular tachycardia (VT) PES will duplicate the VT in 35 per cent[29] or 58 per cent to 67 per cent (Table II See also Table IV) but VT will not be produced in normal hearts (Table II) Sometimes the heart must be primed to respond to PES with VT by prior prolonged rapid pacing PES during pacing at rates above 100 b p m exercise or isoproterenol infusion especially in the presence of partially protective antiarrhythmic regimens

Tachycardias due to automatic foci will not be induced or terminated by PES except possibly

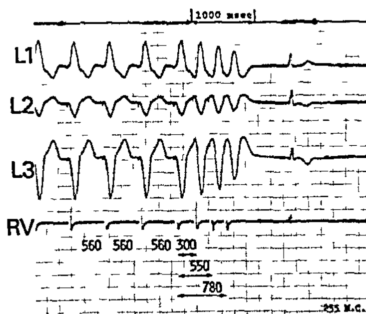


Fig 1 Normal response to triple programmed extrastimuli (PES) During ventricular pacing at 107 b p m (560 msec cycle length) 3 PES are introduced shown here at their respective effective refractory periods 300 550 and 780 msec after the last basic driving stimulus No tachycardia is produced This patient had been referred because of recurrent ventricular tachycardia which could be duplicated by PES until treatment based on serial testing as described in the text

Table II Ventricular tachycardia (VT) due to programmed stimulation or rapid pacing in subjects with and without known VT*

Group†	*VT initiated number tested* By PES‡	*VT initiated number tested* By BRVP§
Patients known to have had VT	14/21(67%)	1/1
Patients without known VT	2‖/77(3%)	0/12
Normal dogs	0/30	–

*Fisher J D Mehra R and Furman S Unpublished data
†Patients on no cardioactive medications and in sinus rhythm or paced at < 110 b p m (< 150 b p m in dogs) None had recent infarcts or correctable metabolic disturbance
‡PES = programmed extrasystoles given at 2 to 4 times diastolic threshold with bipolar electrodes scanning diastole until the refractory period was reached Dogs and patients with known VT received 3 PES if 1 or 2 did not cause VT 32 patients without known VT received 2 or 3 PES
§BRVP = bursts of rapid ventricular pacing 1 to 4 seconds at 300 b p m or maximum rate allowing 1 1 capture
‖Both patients had had repeated syncope not recurring since treated with antiarrhythmic agents 11 and 16 months ago

when related to the slow response [57] Their characteristic response to rapid pacing is either overdrive suppression' often with a gradual return to the baseline rate or overdrive excitation [54 57 59 60] Some tachycardias can be initiated only with rapid pacing often in a series of bursts these may represent automatic tachycardias or rhythms due to the slow response [54 5 6]

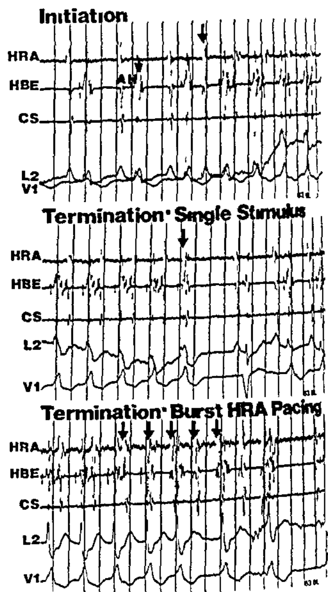


Fig 2 Initiation and termination of SVT *HRA* = high right atrium *CS* = coronary sinus (reflecting left atrial and left ventricular potentials) *HBE* = His bundle electrogram Time lines = 200 msec In the *top panel* SVT is initiated by a single programmed extrastimulus (PES) in the HRA 430 msec after the previous HRA depolarization The SVT could be terminated by a *single* HRA PES 250 msec after the previous HRA beat (middle panel) or by a burst of asynchronous pacing at 190 b p m (*lower panel*) This patient also had Type A WPW

Induction of tachycardia often requires stimulation at rather circumscribed points often identified only by trying the techniques outlined in Table I (Section II A2) at several sites In our series prior to treatment we were able to duplicate the tachycardia in 95 per cent of VT patients and 89 per cent with SVT (supraventricular tachycardia here including those associated with anomalous atrioventricular connections) (Table IV)

The degree of difficulty in initiating a tachycardia can be semi quantified on the basis of (1 the number of PES or the rate and duration o

Table III Patient profile

	VT (19 patients)	SVT* (18 patients)
range (mean)	13 86(5?)	1 81(57)
x Male/Female	15/4	9/9
history in months range (mean)	0 5 216(30)	0 5-43?(136)
Syncope/dizziness	7/8	?/5
Coronary artery disease	13	4
–aneurysm	3	0
myopathy	1	1
Other diseases		2
Unknown/Idiopathic	3	11
tachycardia rate in b p m range (mean)	110-300(191)	1?5-205(15?) V rate 1?5 300(181) A rate

*Including five with manifest pre-excitation and two with anomalous atrioventricular connections revealed by electrophysiologic testing

pacing or amount of isoproterenol required for induction (2) the duration of the "window" or within the cycle when PES will result in tachycardia One can estimate whether drugs or pacemaker modes and rates are beneficial or protective by their effect on the degree of difficulty in reinduction of tachycardia Because some drugs a long duration of action it is not always possible to determine the best antiarrhythmic regimen in one day therefore many patients undergoing an antiarrhythmia protocol will have a temporary electrode left in place for several days of testing

Observations during tachycardia

At surgery epicardial mapping during tachycardia can localize the focus or define the reentry pathways allowing appropriate surgical interventions In the catheterization laboratory patient toleration of the tachycardia is the first consideration and once established important observations can be made An electrode in position to record the His Bundle potential will aid in differentiating VT from SVT A probing recording electrode can be moved to locate the focus of a tachycardia In one of our VT patients we were able to demonstrate that the earliest site of endocardial depolarization was about 1 0 cm away from a previously implanted permanent lead which had been suspected as the cause of the arrhythmia Removal of the permanent lead did not alter the characteristics of the VT but the remaining halo of tissue reaction may have played a role in this VT

Table IV Induction and termination of tachycardia during testing without medications

	VT (19 patients)	SVT (18 patients)
Duplication of tachycardia		
–by 1/2/3 PES† during NSR or slow pacing	3/4/7	9/5/0
–by 1/2/3 PES with pacing > 100 bpm‡	0/0/1	0
–by 1/2/3 PES with Isoproterenol	0/0/1	0
–by bursts of rapid pacing‡	1	2
–by increasing rate then abrupt halt‡	0	0
–by inhibition of permanent pacer	1	0
–total	18 (95%)	16 (89%)
Duplication of tachycardia not achieved	1 (5%)	2 (11%)
Termination of tachycardia		
–1/2/3 PES (total attempted)	2/1/1(9)	8/0/0(10)§
–slow asynchronous pacing (total attempted)	1(?)	4(5)
–overdrive < 30 b p m above tachy rate (total attempted)	1(6)	1(?)
–bursts of rapid pacing (total attempted)	13(15)	9(9)
–DC cardioversion always (usually) required	1(2)	0(0)
–Always spontaneous	4	2

Duplication in the laboratory of the rate and ECG configuration of patient spontaneous tachycardia (initial studies, without medication) The tachycardia could not be duplicated in one VT patient with accelerated idioventricular rhythms at 80 to 110 b p m of the two SVT patients not induced one was on therapy and in the other flutter instead of PAT was induced

†PES = programmed extrastimuli

‡These techniques often became necessary as serial testing continued and the patients were on partially protective regimens

§Among SVT patients atrial or ventricular PES could be used in four (two had evidence of anomalous pathways) Tachycardia in one patient with concealed anomalous pathway could be stopped *only* with V PES or V pacing

Strategic placement of several recording leads can also provide effective endocardial mapping and accurate diagnosis of the arrhythmia (Fig 5) Use of multiple leads also permits the study of conduction sequences during sinus rhythm and in response to extrastimuli at various sites which is particularly helpful in ruling out concealed anomalous atrioventricular pathways Extrastimuli during VT may alter the configuration in such a way as to suggest participation of the bundle branches in the reentry circuit and lead to interruption of the circuit by sectioning the bundle branch

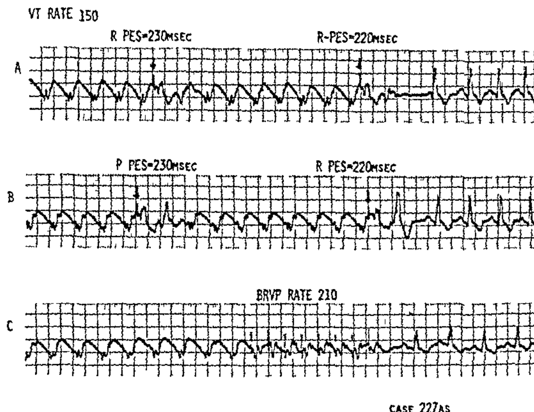


Fig 3 Ventriculuar tachycardia confirmed by intracardiac recordings *Panels A* and *B* demonstrate that a reproducible but narrow window exists where a programmed extrastimulus (PES) 220 msec after the preceding QRS will terminate the VT while 230 msec fails and the refractory period is 215 msec With such a narrow termination window competitive pacing at 70 b p m (in effect random extrasystoles) could require considerable time before terminating the episode A burst of rapid ventricular pacing (BRVP) as in *panel C* was reliably and immediately effective

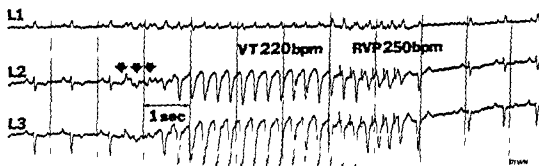


Fig 4 Ventricular tachycardia is initiated by three programmed extrastimuli (*arrows*) and quickly terminated by rapid ventricular pacing (*RVP*) The ability to control induced tachycardias rapidly without DC cardioversion is one of the cornerstones permitting serial testing until a therapeutic regimen is identified *which restores* the patient s response to that shown in *Fig 1*

Termination of tachycardia

Interestingly many of the same pacing techniques useful for induction of tachycardias can also be used for termination (Table I part IC) Bursts of rapid pacing are very effective for both VT[19,2] and SVT[3,24] (Table IV) but reveal less than PES If a tachycardia can *be terminated* by a single PES and the window is found to be large, the patient may be able to terminate his own tachycardia by manually activating a standard 'off the shelf' pacer[17,18] This may be confirmed in the laboratory by asynchronous pacing during tachycardia We have found that bursts of rapid pacing will terminate virtually all tachycardias which also respond to 2 to 3 PES Since implantable units capable of multiple and adjustable PES are not yet available, permanent pacing in patients who require 2 to 3 PESs would at present involve special *units capable of* rapid rates[1,3] For use with VT these units must be preset both in the rate and duration of the burst to minimize *the risk* of accelerating the tachycardia[1] Permanent pacers for VT should be reserved for patients in whom other approaches

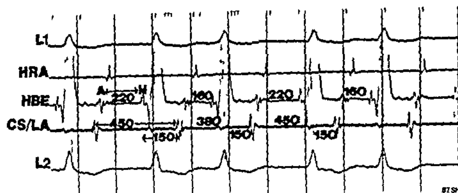


Fig 5 Intracardiac mapping made possible by multiple atrial leads *HRA* = high right atrium *HBE* = His bundle electrogram (with low medial right atrial A wave) *CS/LA* = coronary sinus lead recording primarily a left atrial deflection Time lines are 200 msec This SVT is irregular due to alternating A H times reflecting dual AV nodal pathways The V to LA time remains constant at 150 msec The atrial sequence is LA low RA HRA which might suggest an automatic LA focus this is ruled out however by the irregularity of LA LA intervals further the V to LA interval remains constant implying an anomalous pathway Diagnosis Reentry tachycardia due to concealed anomalous left sided atrioventricular connection with retrograde (V A) conduction and incidental dual AV nodal pathways

have failed and in whom the VT has been terminated many many times without evidence of acceleration or ventricular fibrillation (VF) Unless they are subject to almost immediate syncope or hemodynamic decompensation patients with permanent pacers for termination of VT or SVT by competitive ventricular pacing should ideally go to the hospital for pacer termination to avoid the risk of ventricular fibrillation at home

Serial testing

Only a limited number of drugs can be tested in one day and the effectiveness of intravenous medications should be confirmed when the patient is on oral preparations Using a temporary lead left in place after the initial study serial testing can be performed over several days to answer the questions Will any available drug combinations of drugs or pacer mode rate or site or combination of drugs and pacers make induction of tachycardia impossible or more difficult or actually favor the appearance of tachycardia or make it more malignant in rate or physiologic consequences? In our patients intravenous agents used were edrophonium 5 mg every two minutes for three doses or until protection occurred with testing between each dose and if this agent seemed useful the patient was begun on oral pyridostigmine lidocaine 50 mg every one to two minutes up to a maximum of three doses—the use of this agent is anticipatory as an oral version of lidocaine is not yet available

Table V Patient responses and acceptance of testing

	VT (19 patients)	SVT (18 patients)
Tachycardia duplicated	18	16
Pacer termination of tachycardia during study ≥ once	13†	16†
Serial electrophysiologic pharmacologic testing		
—until confirmation of final regimen	13	14
—stopped prior to confirmation on oral drugs due to other clinical problems fever refusal etc	5	4
Serial pharmacological testing after initial testing	1	0
Patient dropped out of study declined prescribed treatment or regimen changed by other M D	3	3

Spontaneous episodes n one additional patient
†Spontaneous termination in others except o e VT patient who required DC card v rs on

procainamide 7½ to 10 mg per kg was given over 15 minutes with careful attention to blood pressure quinidine 5 mg per kg was given carefully over 20 minutes propranolol was given 1 to 2 mg every two minutes up to a maximum of 7 mg unless the patient had a history of congestive heart failure in which case a maximum of 5 mg was given diphenylhydantoin 750 mg was administered over 45 minutes and digoxin 0 5 mg was administered with a pause of 45 minutes to

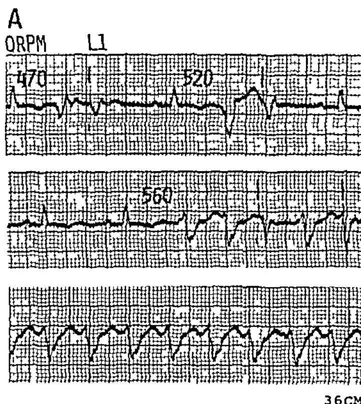


Fig 6 A Problems with automatic antiarrhythmia pacers Tachycardias can often be aborted by automatic programmed extrastimuli (PES) after spontaneous prematures which would otherwise go on to sustained tachycardia ORPM = orthorhythmic pacemaker Patient with multifocal VPCs followed by PES The late VPC initiating VT was not followed by a PES because the pacer had to allow for sinus rates up to 110 b p m so PES followed only when cycle length was under 550 msec

one hour before attempts at induction of tachycardia As far as possible intravenous use of digoxin diphenylhydantoin and quinidine was avoided, these drugs being used on subsequent days of testing after oral loading doses If atropine 1 mg proved useful oral propantheline was tested, bretylium 350 to 400 mg intravenously and 400 mg orally every four hours was also used The sequence of drugs used depended on the patient's clinical status and his previous therapy but in general the use of long acting agents such as propranolol and diphenylhydantoin were preferred to the use of short acting drugs such as procaineamide Attempts at arrhythmia induction during atrial and ventricular pacing at physiologic rates before and after drug administration helps to determine whether protection is enhanced by pacing Once an effective combination is discovered, serial testing on oral preparations is required for titration of dosages and schedule of drug administration

If no combination of drugs or pacer modes offers protection, attention may then be concentrated on establishing a safe and effective pacer mode for rapid termination of the tachycardia, suitable for long term use with an implanted pacemaker Great care must be taken to assure that the pacer mode for termination of a tachycardia proposed for use at home is safe

When prolonged, serial testing can be a grueling experience Patient acceptance (Table V) was generally best among the most symptomatic patients, and was aided by our ability to terminate most tachycardias (100 per cent of SVT and over 90 per cent of VT episodes) by pacer techniques rather than direct current cardioversion (Table IV)

We have been struck by the unpredictability of effective treatment (Table VI) The number of spontaneous ventricular premature beats is a useful guide only in some patients,[1] and there are patients in our series who were without prematures between episodes of VT It has been suggested[61] that in patients with VT induced and terminated by PES that procaineamide is often protective and that propranolol is unlikely to be effective yet in our series we have successfully treated four such patients with propranolol either alone or in combinations excluding procaineamide or quinidine Occasionally it may be prudent to settle for less protection (as estimated from the degree of difficulty in initiating tachycardia) if the resulting tachyarrhythmia is less malignant in rate or hemodynamic effect than another regimen which appears to offer more protection if the tachycardia recurs at home its rate should at least permit survival until the patient reaches the hospital

The long term efficacy of treatment based on serial electrophysiologic pharmacologic testing is very encouraging[51] (Table VII) Patients who were felt to be protected have had significant reductions in numbers and severity of episodes (Table VII), four patients stopped taking their antiarrhythmic medications and had recurrent tachycardias until their regimens were resumed None of our 37 patients has required surgery except for pacer implantation although most had been referred for apparently refractory arrhythmias or life threatening rhythms which occurred so infrequently that waiting in the hospital for spontaneous episodes would be an economically prohibitive method of testing antiarrhythmic regimens Three patients whose VT was associated with aneurysms had originally



Fig 6 B During established tachycardia programmed extrasystoles, (PES) or bursts of pacing can be automatically introduced at fixed intervals or at a preset percentage of the tachycardia cycle length as shown here However while sensing was good during sinus rhythm there was double sen ing (? QRS & T) during VT resulting in stimulation at 45 per cent of the cycle length inst ad of the programmed 90 per cent For explanation see legend for *Fig 6 A*

Table VI Antiarrhythmia regimens prescribed after serial testing

	VT								*SVT*					
						Pacer also†						*Pacer also*		
	CAD	*CM*	*Idio*	*Etc*	*MEDD*‡	*Prevent*	*Slow term*	*BRP*	*PAT or AVNT*	*AnAVC*	*MEDD*	*Prevent*	*Slow term*	*BRP*
Single drugs														
Digitalis (D)	–	–	–	–	0 275 ± 07	–	–	–	3§	–	0 244 ± 01	–	–	1
Pyridostigmine ‖	–	–	–	–	–	–	–	–	1	1	540	–	–	–
Propantheline ‖	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Propranolol (P)	1	–	–	–	213 ± 42	–	–	–	1	1	123 ± 31	–	–	1
Diphenylhydantoin (DPH)	1	–	1	–	78 ± .2	1	1	–	–	–	300	–	–	–
Procaine Amide (PA)	2	–	–	–	3 33 ± 911	–	–	–	1	–	2000	–	–	–
Quinidine (Q)	–	–	–	–	1193 ± 77	–	–	–	–	–	1167 ± 203	–	–	–
Bretylium (B)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pacer Only	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Multiple drugs														
P & DPH	–	–	–	1		1	–	1	–	–				
P & DPH & D¶	4	–	–	–		–	–	–	–	–		–	–	–
P & DPH & D & PA	2	–	–	–		–	–	–	–	–		–	–	–
P & DPH & PA	–	–	–	1		–	–	–	–	–		–	–	–
P & PA & D	–	–	–	–		–	–	–	–	–		–	–	–
P & D	1	–	–	–		–	–	–	–	1		1	1	–
P & Q	–	–	1	–		–	–	–	2	–		–	–	–
P & Q & D	–	1	–	–		–	–	–	–	2		1	2	–
Q & D	1	–	–	–		–	–	1	–	1		1	1	–
PA & D	1	–	–	–		–	–	–	–	–		–	–	–
D & DPH	–	–	–	–		–	–	–	1	–		–	–	–
						–	–	–	1	–		–	–	–

*CAD = coron ry artery disease CM = card omyopathy Id o = idiopathic Etc = miscellaneous. Among VT pts 1 with prolonged QT 1 with Chagas disease 2 SVT pts had rheum tic he rt disease PAT = trial t chycardia AVNT = AV nod l (junctional) ta hy ardia AnAVC = an ma lous AV connection.

†Prev nt. = tachy ard (T) pre ted b tandard pa er S ow term = T terminated by competitive pacing at physiologic rates by ordinary pacer BRP = T term. by bursts of rapid pacing

‡MEDD = mean effective d ily dose (mg ± S D) for all p ti nts wheth r n singl or mult ple drugs.

§Numbers re patients treated w th this regim n

‖Pyridostigmine (Mestinon) rally after edrophonium (Tensilo) intravenously and propantheline (Pro-Banthine) orally after atropine intravenousl Although atropine or bretylium intrav nously wa protect e in several cases, lternate ffecti e drugs were chosen for long term treatment.

¶Digitalis when not used lone was ften necessary fo treatment f CHF and in such cases its antiarrhythmic role is unknown Several patients also had pacers for brady rdia their role in prev ting ta hy rd is peculative nd they are not listed here

Table VII Follow up of treated patients with recurrent tachycardia

	VT *(19 patients)*	*SVT* *(18 patients)*
Degree of control		
0 0 25% reduction of episodes	1	1
1 25 50% (not considered improved)	0	2
2 50-90%/or reliable pacer termination	0	1
3 > 90%/or asymptomatic unsustained tach	1	4
4 100%	15	8
Mean	3 7	3 1
Episodes per month† prior to/after testing ± SD (p‡)	2 2 ± 1 9/0 003 ± 01(< 001)	4 6 ± 5/1 4 ± 3(< 05)
Hospitalizations per year† prior to/after testing ± SD (p)	2 3 ± 1 8/0(< 001)	1 9 ± 1 8/0 08 ± 0 3(< 005)
Holter after discharge showed sustained/unsustained/no tachycardia (No pts)	0/1/12(13)	0/1/9(10)
Months follow up range (mean ± S D)†	1 24(6 ± 6)	2 17(9 ± 5 6)
Patients§ controlled by 1/2/3/4 drugs alone (mean)	4/4/6/2(2 4)	6/4/0/0(1 4)
Patients controlled by 1/2/3/4 drugs (mean) and pacer	1/1/0/0(1 5)	2/3/1/0(1 5)
Drugs and Pacer preventative/terminating/both	0/1/2	0/3/3
Pacer termination slow competition/BRP‖	1/2	4/2

Grade based on detailed patient interview hospital records physician records Holter monitor Excludes 2 VT and 2 SVT patients who were not treated for various reasons
†Among patients for whom treatment was established (18 VT 16 SVT) and who adhered to regimen (15 VT pts 13 SVT) Uncountably large numbers of episodes entered as 5 Some episodes represent clusters of tachycardias including those requiring cardioversion
‡(p by paired T test)
§Patients for whom a regimen was established (18 VT 16 SVT)
‖BRP bursts of rapid pacing Pacers in this table are implanted

been referred for surgery but were rejected because residual ventricular function was poor, two are doing well on therapy but one has succumbed to congestive heart failure

Horizons

We await the equivalent of an implantable demand pacer for tachyarrhythmias Presently implanted units for terminating tachycardias must be manually activated by application of a magnet or radio frequency transmitter Some patients however experience syncope with the onset of tachycardia or are unaware of their tachyarrhythmia until symptoms such as congestive failure appear Such patients would welcome an automatic pacer which would respond appropriately to terminate the episode Temporary units are available which are designed to automatically abort or terminate tachycardias[13 15 30] but sensing problems must be overcome for use in implantable automatic antiarrhythmic pacers (Fig 6) The development of automatic implantable units is further complicated by the need for individualized responses to each patient s tachycardia The costs of modern chip circuitry are excessive if a given circuit is used in only a few units The possibility of a single chip capable of multiple programming exists but the chances of malfunction may then be increased Bioengineers may thus hold the key to the next stage in pacer control of tachycardias

Summary

The place of pacemakers in the treatment of tachyarrhythmias has expanded far beyond the initial role in the brady tachy syndrome of providing a minimum guaranteed rate while medications suppress the tachycardia Techniques have been developed for prevention termination and duplication of a patient s spontaneous tachycardia under safe catheterization laboratory conditions Combined with accumulating information about the normal responses to electrophysiologic stresses these techniques have led to a new dimension in arrhythmia control Most tachycardias previously felt to be refractory

in be controlled after serial electrophysiologic narmacologic testing during which sequential narmacologic and pacer regimens are tested a combination is found which prevents duction of tachycardias and/or a pacer mode is und which reliably terminates the tachycardia se of such an approach reduces hospital admis ons and referral for surgery and eliminates prolonged hospitalization for assessment of thera y in patients with infrequent but potentially thal spontaneous tachycardias

Note

A word of caution the stimulation techniques used in the evaluation and control of tachyar rhythmias must be employed with extreme caution In the testing laboratory the side effects of intravenous drugs must be known and there must be provisions for immediate DC cardiover sion and resuscitation Before a permanent pacer for termination of tachycardia is implanted scores of episodes should have been successfully t eated with a temporary unit When possible patients with permanent ventricular pacers for termination of tachycardia should go to the hospital before activating their pacers The families of all patients with recurrent tachyar rhythmias should be instructed in cardiopul monary resuscitation With these precautions both testing and treatment can be safe (we have had no pacer related deaths in our series) as well as effective

The authors wish to express their gratitude to Ms Robin Orlansky for her patience as well as for her typing and to Mrs Maureen Eisenmann for the fine illustrations

REFERENCES

1 Lown B Temte J V Reich, P Gaughan C Regestein Q and Hai H Basis for recurring v ntricular fibrillation in the absence of coronary heart disease and its management N Engl J Med 294 6 3 19 6
2 Winkle R A Alderman E L Fitzgerald J W and Harrison D C Treatment of recurrent symptomatic ventricular tachycardia Ann Intern Med 85 1 1976
3 Gallagh r J J Sealy W C Kasell J and Wallace A G Multiple accessory pathways in patients with pre exci at on syndrome Circulation 64 571 1976
4 Lloyd R Okada R Stagg J Anderson R Hattler B and Marcus, F The treatment of recurrent ventricular tachycard a with bila eral cervico thoracic sympathetic ganglionectomy Circulation 50 387 19 4
5 Ba ta L L Takeshita A Theilen E O and Ehrenhaft J L Aneurysmectomy in treatment of ventricular and supraventricular tachyarrhythmias in patients with postinfarction and traumatic ventricular aneurysms, Am J Cardiol 32 693 1973
6 Ricks, W B Winkle R A, Shumway N E, and Harrison D C Long term results of surgical therapy for refractory ventricular arrhythmias (Abstract) Am J Cardiol 37 166 1976
7 Spurrell R A J Sowton E and Deuchar D C Ventricular tachycardia in 4 patients evaluated by programmed electrical stimulation of heart and treated in 2 patients by surgical division of anterior radiation of left bundle branch Br Heart J 35 1014 1973
8 Haft J I Treatment of arrhythmias by intracardiac electrical stimulation Progr Cardiovasc Dis 16 539 19 4
9 Rubenstein J J Schulman C L Yurchak, P M and DeSanctis R W Clinical spectrum of the sick sinus syndrome Circulation 46 5 1972
10 Johnson R A Hutter A M DeSanctis R W Yurchak P M Leinbach R C and Harthorne J W Chronic overdrive pacing in the control of refractory ventricular arrhythmias Ann Intern Med 80 380 1974
11 Friedberg C K Lyon L J and Donoso F Suppression of refractory recurrent ventricular tachycardia by transvenous rapid cardiac pacing and antiarrhythmic drugs AM HEART J 79 44 19 0
12 Sowton E Leatham A and Carson P The suppression of arrhythmias by artificial pacemaking Lancet 2 1098 1964
13 Gurtner H P, Gertsch, M and Zacouto F Orthorhythmischer herzschrittmacher und salvenformige herzstimulation Schweiz Med Wochenschr 105 33 1975
14 Ludentz, B Steinbeck G Guize L and Zacouto F Schrittmachertherapie tachykarder rhythmusstorungen durch frequenzbezogene intervallstimulation Dtsch Med Wschr 100 730 19 5
15 Zacouto F Guize L J Fontaine G H Gerbaux A J Improved control of recurrent tachycardias by automatic orthorhythmic pacing (Abstract) Circulation 50 III 59 1974
16 Escher D J W and Furman S Emergency treatment of cardiac arrhythmias J.A.M.A 214 2028 1970
17 Moss A J and Rivers Jr R J Termination and inhibition of recurrent tachycardias by implanted pervenous pacemakers, Circulation 50 942, 1974
18 Abinader E G Recurrent supraventricular tachycardia J.A.M.A 236 2203 1976
19 Bennett M A and Pentecost B L Reversion of ventricular tachycardia by pacemaker stimulation Br Heart J 33 922 1971
20 Fontaine G Frank, R Beneton H Vedel J Lehlond J B Grosgogeat Y and Welti J J Interet d une sonde endocavitaire temporaire pour le diagnostic et l interruption d une crise de tachycardie ventriculaire apres infarctus du myocarde Ann Cardiol Angeiol 22 3 1 1973
21 Fisher J D Furman S and Mehra R Ectopic ventricular tachycardia treated with bursts of pacing at 300 per minute from an implanted ventricular pacer (Abstract) Circulation 52 II 187 19 5
22 Furman S Fisher J D and Mehra R Termination of ventricular tachycardia with bursts of rapid ventricular pacing (Abstract) Circulation 54 II 3 1976
23 Kahn A Morris J J and Citron P Patient initiated rapid atrial pacing to manage supraventricular tachycardia Am J Cardiol 38 200 19 6
24 Spurrell R A J and Sowton E Pacing techniques in the management of supraventricular tachycardias J Electrocardiol 8 287 1975
25 Wellens H J J Programmed el ctrical stimulation of the heart in the study and treatment of tachyarrhythmias Leiden 19 1 J E Stenfert Kroese

26 Wellens H J J Schuilenburg R M and Durrer D Electrical stimulation of the heart in patients with ventricular tachycardia Circulation **46** 216 1972

27 Wellens H J J Lie K I and Durrer D Further observations on ventricular tachycardia as studied by electrical stimulation of the heart Circulation **49** 647 1974

28 Wellens H J J Duren D and Lie K I Observations on mechanisms of ventricular tachycardia in man Circulation **54** 237 1976

29 Denes P Wu D Dhingra R C Amat y Leon F Wyndham C Mautner R K and Rosen K M Electrophysiological studies in patients with chronic recurrent ventricular tachycardia Circulation **54** 229 1976

30 Spurrell R A J and Sowton E The management of paroxysmal supraventricular tachycardia using a scanning pacemaker system Fifth International Symposium on Cardiac Pacing Tokyo 1976 p 41

31 Waldo A L MacLean W A H Karp R B Kouchoukos N T and James T N Continuous rapid atrial pacing to control recurrent or sustained supraventricular tachycardias following open heart surgery Circulation **54** 245 1976

32 Cantwell J D Weaver W T and Fletcher G F Paroxysmal atrioventricular junctional tachycardia J A M A **216** 1860 1971

33 Krikler D M and Goodwin J F (ed) Cardiac arrhythmias the modern electrophysiologic approach London 1975 W B Saunders

34 Svenson R H Gallagher J J Sealy W C and Wallace A G An electrophysiologic approach to the surgical treatment of the Wolff Parkinson White Syndrome Circulation **49** 799 1974

35 Zipes D P DeJoseph R L and Rothbaum D A Unusual properties of accessory pathways Circulation **49** 1200 1974

36 Wellens H J and Durrer D Patterns of ventriculo atrial conduction in the Wolff Parkinson White Syndrome Circulation **49** 22 1974

37 Spurrell R A J Krikler D M and Sowton E Problems concerning assessment of anatomical site of accessory pathway in Wolff Parkinson White Syndrome Br Heart J **37** 127 1975

38 Gallagher J J Cope G D Tonkin A M and Wallace A G Retrograde atrial preexcitation following premature ventricular beats during reciprocating tachycardia in the Wolff Parkinson White Syndrome (Abstract) Am J Cardiol **37** 138 1976

39 Gallagher J J Sealy W C Kasell J and Wallace A G Multiple accessory pathways in patients with the pre excitation syndrome Circulation **54** 571 1976

40 Kupersmith J Electrophysiologic mapping during open heart surgery Progr Cardiovasc Dis **19** 167 1976

41 Boineau J P Moore E N Spear J F and Sealy W C Basis of static and dynamic electrocardiographic variations in Wolff Parkinson White Syndrome Am J Cardiol **32** 32 1973

42 Boineau J P Moore E N Sealy W C and Kasell J H Epicardial mapping in Wolff Parkinson White Syndrome Arch Intern Med **135** 422 1975

43 Frank R Guiraudon G Fontaine G Grosgogeat Y Cabrol C and Facquet J Updated results in surgical treatment of recurrent ventricular tachycardia oriented by ventricular activation mapping in 8 patients without coronary artery disease (Abstract) Am J Cardiol **37** 136 1976

44 Frank R Haiat R Fontaine G Grosgogeat Y and Guiraudon G Ventricular epicardial mapping in a case of left ventricular conduction disturbances due to an old myocardial infarction Adv Cardiol **14** 87 1975

45 Spurrell R A J Yates A K Thorburn C W Sowt. G E and Deuchar D C Surgical treatment of ventric ular tachycardia after epicardial mapping studies, Br Heart J **37** 115 1975

46 Boineau J Bilitch M Zubiate P Ricketts, H, Kafrumi G and Mooney C Mapping cardiac excita and surgical intervention in patients with ventric arrhythmias (Abstract) Circulation **51** and **52** II 15 1975

47 Fontaine G Guiraudon G Frank R Gerbaux, L, Cousteau J P Barrillon A Gay J Cabrol C and Facquet J La cartographie epicardique et le traitement chirurgical par simple ventriculotomie de certaines tachycardies ventriculaires rebelles par reentree Arch Mal Coeur **68** 113 1975

48 Gallagher J J Oldham H N Wallace A G Pet R H and Kasell J Ventricular aneurysm with ventric ular tachycardia Am J Cardiol **35** 696 19 5

49 Wu D Wyndham C Denes P Miller R and Rose K Chronic electrophysiological study of patients with paroxysmal tachycardia (Abstract) Clin Res **24** 24 A 1976

50 Wu D Denes P Miller R Simpson R and Rosen K M Electrophysiological studies with multiple drugs in patients with reentrant tachycardias due to concealed extranodal pathways (Abstract) Circulation **53** and **54** II 188 1976

51 Fisher J D Mehra R Furman S Escher D J W and Cohen H Serial electrophysiologic pharmacologic testing for control of recurrent tachyarrhythmias in 38 patients (Abstract) Am J Cardiol (In press 1977)

52 Han J The concepts of reentrant activity responsible for ectopic rhythms Am J Cardiol **28** 253 1971

53 Vassalle M Automaticity and automatic rhythms, Am J Cardiol **28** 245 1971

54 Cranefield P F Wit A L and Hoffman B F Gene of cardiac arrhythmias Circulation **47** 190 1973

55 Schamroth L The pathogenesis and mechanism o ventricular arrhythmias in Progress in Cardiology 3 Yu P N and Goodwin J F editors Philadelphia 19 Lea & Febiger p 75

56 Strauss H C Saroff A L Bigger Jr J T ar Giardina E G V Premature atrial stimulation as a ke to the understanding of sinoatrial conduction in mar Circulation **47** 86 1973

57 Goldreyer B N Gallagher J J and Damato A N The electrophysiologic demonstration of atrial ectop tachycardia in man Am Heart J **85** 205 1973

58 Wit A L Cranefield P F Triggered activity in cardia muscle fibers of the simian mitral valve Circ Res **38** 8 1976

59 Hogan P M Wittenberg S M and Klocke F J Relationship of stimulation frequency to automaticity i the canine Purkinje fiber during Ouabain administratio Circ Res **32** 377 1973

60 Vassalle M Cummins M Castro C and Stucke J H The relationship between overdrive suppressio and overdrive excitation in ventricular pacemakers i dogs Circ Res **38** 367 1976

61 Wellens H J Lie K I Durrer D R and Dohma H J Effect of procainamide propranolol and verapam on mechanism of tachycardia in patients with chron recurrent ventricular tachycardia Circulation **53** ar **54** II 230 1976

fever endocarditis—A case occurring in the nited States

epeatedly sterile blood cultures occur in 15 to 20 per cent of patients with infective endocarditis In this setting potential causative microorganisms are Hemophilus Brucellae Chlamydiae Mycoplasms anaerobes fungi, Coxsackie virus and Coxiella burnetii Although uncommon endocarditis caused by C burnetii is well recognized in the British Isles and in Australia. We are reporting this case to alert the American physician to consider the possibility of endocarditis caused by this agent in the appropriate setting

The patient a 39 year-old native Korean was hospitalized because of increasing exertional dyspnea of one month duration. Anemia, cardiomegaly aortic systolic and diastolic murmurs, and hematuria were noted There was no history of illness or heart disease

Examination revealed a thin afebrile man whose blood pressure was 170/40 mm Hg pulse 110/minute regular Left ventricular hypertrophy was present P was increased Murmurs of aortic and mitral insufficiency were present There were bibasilar rales but no hepatosplenomegaly or signs of peripheral emboli Laboratory values included a hematocrit of 33 per cent normal white blood count ESR of 98 mm hr normal urinalysis and a serum globulin of 4 9 Gm The chest x-ray demonstrated congestive heart failure

Eight blood cultures were obtained and therapy was begun with aqueous penicillin G and streptomycin as well as digoxin and lasix During the ensuing four days conjunctival and multiple splinter hemorrhages, hematuria and splenomegaly were detected

Over the next week there was symptomatic improvement No new peripheral lesions were noted and the spleen decreased in size As all blood cultures remained sterile serologic tests for brucella coxsackie virus and C burnetii were obtained The titers for Phase I and II complement fixing antibodies to C burnetii were later reported positive 1/32 and 1/4 respectively

On the twelfth hospital day cardiac catheterization was performed to assess the degree of mitral insufficiency preparatory to valve replacement The left ventricular and aortic diastolic pressures were 40 mm Hg without evidence of aortic stenosis As the catheter traversed the aortic valve the patient suffered a right hemiparesis Despite intensive treatment decreasing urinary output with progressive metabolic acidosis ensued and he died on the seventeenth day

Postmortem examination revealed a cardiac weight of 55 Gm and a hypertrophied dilated left ventricle with softening of its anterior wall indicating early infarction The latter was confirmed histologically There was a large partially calcified vegetation on the non-coronary aortic cusp occluding the orifice of the left main coronary artery The left coronary cusp was almost entirely destroyed. The coronary arteries were widely patent There was pulmonary congestion large infarcts in the spleen and kidneys areas of encephalomalacia but no hepatitis The heart had been briefly immersed in formalin prior to bacteriologic investigation and cultures of the aortic valve were sterile No microorganisms were noted with hematoxylin and eosin Giemsa or fungal stains Fragments of the emulsified aortic valve were inoculated into guinea pigs C burnetii were not isolated after several serial passages nor did these animals develop antibody titers. Serum obtained post mortem was examined for complement fixing antibody titers to Phase I and II of C burnetii which were diagnostically elevated at 1 32 and 1 64 respectively

Q fever has been a well recognized clinical entity since Derrick's initial investigation in 1937 of a febrile illness in Brisbane meat packers. After inhalation of infected aerosols a self limited respiratory illness develops Occasionally patients develop protracted illness with hepatitis and rarely endocarditis Following Evan's report in 1958 C burnetii endocarditis became well recognized in England There are two isolated references to the clinical association of Q fever and endocarditis occurring in the United States In neither patient was the organism isolated from the valvular vegetation nor was fourfold rise in specific antibody titer demonstrated

In contrast to classic subacute bacterial endocarditis affected males outnumber females by a ratio of 6 1 with 90 per cent of patients having prior cardiac disease particularly aortic stenosis or insufficiency The relatively high incidence of aortic valve involvement (80 per cent) by this agent and infrequency of hematuria are noteworthy but unexplainable Three such infections have occurred on prosthetic heart valves

Although elevations in the complement fixation titers to Phases I and II antigens are confirmatory laboratory indicators of Q fever in at least one proven case only Phase II titers were increased Andrews and Marmion stress that Phase I complement fixing antibodies are markers of chronic Q fever infections such as endocarditis and are considered important diagnostic criteria. The elevation of the Phase I titers in our patient in the absence of pathologic evidence of hepatitis thus significant and confirmatory of disease due to this agent The fourfold rise in Phase II titers in our case suggests an active infection due to C burnetii and is consistent with the post mortem findings

In 1967 following the report of five patients apparently cured by valve replacement surgical management was advocated as definitive therapy To date a reported total of eight patients with Q fever endocarditis have been subjected to surgical intervention because of intractable heart failure with an operative mortality rate of 38 per cent Of thirteen patients treated medically with tetracycline eight (61.3 per cent) have died Small numbers of patients in either group allow no definitive conclusions regarding optimal management

Performed by Dr Grace Ka of the Department of Path l gy

Microcolonies of *C burnetii* have been observed in but 62 per cent of cases in which they were sought[2,4,6,7,13,1,7,18,20] The reasons for failure of histologic demonstration of organisms are unclear Laboratory isolation has been successful in 83 per cent of instances[3,6,2,7] Failure to isolate *C burnetii* or to demonstrate serologic evidence of infection in guinea pigs inoculated with fragments of the aortic valve from our patient may relate to the inactivating effect of formalin

In summary the typical patient with *C burnetii* endocarditis is a middle aged man with known valvular heart disease usually aortic who experiences a self limited influenzal like illness 6 to 16 months previously The presenting manifestations are malaise low grade fever clubbing splenomegaly and signs and symptoms of congestive failure Mild to moderate anemia is present with a normal leukocyte count Hematuria is infrequent although proteinuria is common Clinical evidence of hepatitis is rare Blood cultures for common microorganisms are persistently sterile The diagnosis is substantiated by an elevation of complement fixing antibodies to Phase I and II antigens of *C burnetii* The patient often responds poorly to high doses of penicillin and streptomycin but occasionally responds well to tetracycline The large size of the vegetation may require surgical intervention to correct the hemodynamic lesion Physicians presented with a case of endocarditis and persistently sterile blood cultures should consider the possibility of infection due to *C burnetii* Appropriate serologic tests should be performed to confirm the diagnosis

The authors wish to thank Dr Theodore E Woodward for his helpful suggestions and review of this manuscript and to Dr Richard A Ormsbee Rocky Mountain Laboratory for performing the guinea pig inoculations

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REFERENCES

1 Lerner P I and Weinstein L Infective endocarditis in the antibiotic era N Engl J Med **274** 199 205 259 265 323 330 388 393 1966
2 Robson A O and Shimmin C D Chronic Q fever I Clinical aspects of a patient with endocarditis Br Med J **2** 980 1959
3 Andrews P S and Marmion B P Chronic Q Fever II Morbid anatomical and bacteriological findings in a patient with endocarditis Br Med J **2** 983 1959
4 Evans A D Powell D E and Burrell, C D Fatal endocarditis associated with Q fever Lancet 1 64 1959
5 Smith W G and Evans A D Chronic Q fever with mitral valve endocarditis Lancet 2 846 1960
6 Marmion B P Higgins F E Bridge J B and Edwards, A T A case of subacute rickettsial endocarditis with a survey of cardiac patients for this infection Br Med J **2** 1264 1960
7 Ferguson I C Craik J E and Grist, N R Clinical virological and pathological findings in a fatal case of Q fever endocarditis J Clin Pathol **15** 235 1962
8 McIver M A case of Q fever endocarditis Med J Aust **2** 379 1962
9 Clinicopathologic conference An unusual case of endocarditis Br Med J **1** 1143 1963
10 Mitchell R, Grist N R Bezaz G and Kennedy A C F Pathological rickettsiological and immunofluorescence studies of a case of Q fever endocarditis J Pathol Bacteriol **91** 317 1966
11 Marmion B P Subacute rickettsial endocarditis An unusual complicatoin of Q fever J Hyg Epid and Microbiol Immunol **6** 79 1962
12 Lamb D C and Grist N R A case of Q fever endocarditis Br Med J **4** 418 1967
13 Kristinsson A and Bentall H H Endocarditis due to Q fever Medical and surgical treatment Lancet 2 693 1967
14 Walters J Rickettsial endocarditis Br Med J **2** 0 1968
15 Meyers D Rickettsial endocarditis Br Med J **2** 71 1968
16 Turck W P and Matthews M B Rickettsial endocarditis Br Med J **1** 185 1969
17 Lamb R Boyd J F and Grist N R Q fever endocarditis Scott Med J **14** 10 1969
18 Morgans C M and Cartwright R Y Case of Q fever endocarditis at site of aortic valve prosthesis Br Heart J **31** 520 1969
19 Hurley B Q fever endocarditis Proc R Soc Med **63** 282 1970
20 Tunstall Pedoe H D Apparent recurrence of Q fever endocarditis following homograft replacement of aortic valve Br Heart J **32** 568 1970
21 Crook B Q fever endocarditis with homograft valve replacements Proc R Soc Med **65** 980 1972
22 Freeman R and Hodson M Q fever endocarditis treated with Trimethoprim and Sulphamethoxazole Br Med J **1** 419 1972
23 Derrick E H Q fever a new fever entity Clinical features diagnosis and laboratory investigation Med J Aust **2** 281 1937
24 Powell O W and Stallman N D The incidence and significance of phase I complement fixing antibody in Q fever J Hyg **60** 359 1962
25 Marmion B P Stoker M G P, McCoy J H and Malloch R A Q fever in Great Britain Lancet 1 503 1963

IgA nephritis unassociated with systemic disease

A study of renal biopsies from cases of glomerulonephritis revealed glomerular deposits of IgA in 8 4 per cent of patients who did not have systemic disease or a well recognized type of nephritis Patients were divided into two groups The first which comprised 4 5 per cent of cases included those with mild histologic abnormalities who were normotensive and had no

renal functional impairment at the time of diagnosis. The second group of patients had more marked histologic changes, hypertension and/or decreased renal function. Microscopic hematuria was present in almost all patients of both groups.

Renal biopsies showed generalized segmental mesangial proliferation to be the most frequent histologic abnormality in both groups. Focal mesangial lesions were noted less often. Biopsies from the second group of patients showed diffuse mesangial abnormalities as well, with hyalinization of a significant number of glomeruli in about one third of cases. Electron dense deposits were present in mesangial regions with rare intramembranous and subendothelial deposits in an occasional patient. Immunofluorescent studies showed IgA to be the predominant immunoglobulin in mesangial areas in both groups of patients. IgG was detected in 50 per cent of cases and IgM in 1? per cent. Secretory component was not found in glomeruli of either group.

C3 and properdin were present in glomeruli in almost all biopsies tested while C4 was never demonstrated. A depression of serum complement components was not detected although one patient had a fall in C3 on two occasions associated with exacerbations of renal disease.

Elevations in serum IgA were found in 50 per cent of patients in the first group and in 20 per cent of the second. The IgA levels were elevated in both groups as were IgA/IgG ratios. The mean secretory IgA values in serum were not elevated in either group of patients.

Follow up revealed persistent microscopic hematuria with normal renal function in all patients of the first group. Hypertension was present in 50 per cent of cases in the second group and an occasional patient had severe proteinuria and decreased creatinine clearance. The precise relationship between the two groups of patients is not known nor are the prognostic factors in individual cases. Progression of the renal disease has been documented in this condition by serial biopsies.

The presence of IgA, C3 and properdin in glomeruli is suggestive of activation of the alternative complement pathway. Aggregated IgA myeloma proteins have been reported to activate the alternate pathway in vitro. The nature of IgA deposits in the kidney and their role in the pathogenesis of glomerulonephritis is unknown. IgA associated nephritis first described by Berger represents a subgroup of the clinical condition idiopathic recurrent hematuria which includes a heterogeneous group of renal diseases.

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REFERENCES

1. Katz A, Underdown B J, Minta J O, and Lepow I H: Glomerulonephritis with mesangial deposits of IgA unassociated with systemic disease. Can Med Assoc J 114:209, 1976
2. McCoy R C, Abramowsky C R, and Tisher C C: IgA nephropathy. Am J Pathol 76:123, 1974
3. Gotze O, and Muller Eberhard H J: The C Activator system. An alternate pathway of complement activation. J Exp Med 134 (Suppl):90, 1971
4. Berger J: IgA glomerular deposits in renal disease. Transplant Proc 1:939, 1969

Failure of autonomic control of cerebral vessels in hypertension—the cause of stroke?

It is now well established that patients with anything more than mild hypertension have a greatly increased incidence of both cerebral hemorrhage and cerebral infarction. It is also known that reduction of the raised blood pressure by appropriate therapy lowers the incidence of both these types of cerebrovascular catastrophe. This strongly suggests that it is the raised blood pressure itself that is responsible for the damage of cerebral vessels leading in turn to hemorrhage or thrombosis rather than any other factor. Postmortem examination of the hypertensive subject shows a number of consistent and interesting features in addition to the expected atheroma. First, the muscle coat of the larger cerebral arteries is much hypertrophied compared to normal. Second, there is a distinct pathological change which affects small intracerebral arteries 50 to 200 μm in diameter. This consists of multiple microaneurysms arising on segments of dilated artery. The wall of these microaneurysms usually shows evidence of accumulation of fibrin and fat in the wall which is referred to as lipohyalinosis. The wall of others presumably at a later stage of development consists only of connective tissue and around them there is frequently evidence of leakage of blood.

Third, in the brain of the chronic hypertensive patient small deep cerebral infarcts are often found. These infarcts are usually associated with occlusion of small intracerebral arteries. Close examination of these arteries reveals that at the site of the thrombotic occlusion there is again evidence of lipohyalinosis. Proximal to the occlusion the vessel is dilated.

Although lipohyalinosis is occasionally found without microaneurysm formation or thrombotic occlusion, they are all found most commonly in high pressure areas, namely the

putamen globus pallidus external capsule thalamus pons and subcortical white matter Regions remote from high pressure such as the centrum semi ovale and cerebellar hemispheres are relatively free from these changes*

Ross Russell[4] has recently advanced the ingenious theory that mechanical distension of the vessels explains lipohyalinosis This damage of the wall leads to thrombosis or because of the raised pressure to microaneurysm formation and eventually to intracerebral hemorrhage It is known that as arterial blood pressure rises cerebrovascular resistance increases in such a way that cerebral blood flow remains constant It is also known (*vide infra*) that at very high pressures this mechanism breaks down and substantial increases of flow occur* Ross Russell suggests that as the vascular resistance gives way more distal vessels which are normally protected from higher pressure become exposed and distended At a certain point the fibrous vessel wall loses its structural integrity and becomes permeable to plasma and fat In turn the lipohyalinosis causes the small artery either to rupture or to become completely occluded

If this hypothesis is true the fundamental question then becomes What causes the normal cerebrovascular resistance to give way? Before this can be answered one has to determine what normally regulates the cerebral vessels Over the last few years evidence has accumulated which shows that cerebral vessels are innervated in a similar fashion to those in other vascular beds This evidence has been recently reviewed The most impressive evidence is morphological and histochemical which makes it clear that in most species there is an adrenergic constrictor pathway originating in the superior cervical ganglion and a dilator pathway which may well be cholinergic carried by the seventh cranial and greater superficial petrosal nerves Unfortunately uncertainty has surrounded the physiological function of these nerves James Millar and Purves however showed in a series of baboon experiments that the actions of the sympathetic vasomotor nerves could not be considered in isolation from those of the dilator pathway and that the importance of both pathways appeared to increase as blood gas tensions and arterial pressure departed from normal Interestingly enough it was found that the effect on the cerebral circulation of sympathetic nerve activity was greatest at high rather than at low arterial pressure It was suggested in that paper that the cerebral vessels were reflexly controlled and that the arterial chemo and baroreceptors were the receptors involved in the afferent loop of the reflex arc

This suggestion was recently confirmed by Ponte and Purves in a further series of baboon experiments They showed that stimulation of the carotid body chemoreceptor invariably caused a rise in cerebral blood flow Stimulation of the carotid sinus baroreceptors caused a fall in blood flow and a fall in carotid sinus pressure caused a rise in flow All these changes were dependent on the integrity of afferent receptor nerves These findings have now been substantiated by other workers °

In patients with chronic hypertension total and regional cerebral blood flow is usually normal under resting conditions If arterial pressure is lowered the discharge from peripheral baroreceptors decreases and vanishes at mean pressures around 40 to 60 mm Hg Associated with this fall in pressure simultaneous cerebral vasodilatation occurs preventing a fall in cerebral blood flow Below pressures of 40 to 60 mm Hg further cerebral vasodilation is not possible From this point a further fall in pressure is accompanied by a fall in flow Strandgaard and colleagues have shown that this phenomenon occurs in the hypertensive patient but the end point is shifted upwards.

An increase in blood pressure on the other hand, is associated with an increased rate of baroreceptor discharge and an increased degree of vasoconstriction of cerebral vessels The net effect of these changes is to ensure constancy of cerebral blood flow and presumably therefore a constancy of oxygen supply to the brain At high levels of blood pressure baroreceptor discharges no longer increase further Strandgaard and colleagues have shown in patients that an upper point was reached beyond which an increase of pressure caused an increase of cerebral blood flow No evidence of vasospasm was found in any patient at high blood pressure It is tempting to place these two pieces of new information together It may well be that the collapse of cerebrovascular resistance that Ross Russell has postulated to be of fundamental importance in the genesis of cerebral infarction and hemorrhage is in fact due to a failure of the normal physiological autonomic nervous system control This system fails because transiently the pressure is too high It is also conceivable of course that in certain situations where dysfunctions of the autonomic nervous system are not unknown i e diabetes that the breakdown point of vascular resistance is reached at a lower level of blood pressure

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REFERENCES

1 Shurtleff D The Framingham Study 16 year follow-up U S Government Printing Office 1970
2 Breckenridge A Dollery C T and Parry E H Prognosis of treated hypertension Changes in life expectancy and causes of death between 1952 and 1967 Q J Med 39 411 1970
3 Adams R D and Van der Eecken H M Vascular diseases of the brain A Rev Med 4 213 1953.
4 Ross Russell R W Observations on intracerebral aneurysms Brain 86 426 1963
5 Fisher C M Lacunes small deep cerebral infarcts Neurology (Minneap) 15 774 1965
6 Ross Russell R W How does blood pressure cause stroke Lancet II 1283 1975
7 James I M Millar R A and Purves M J Observations on the extrinsic neural control of cerebral blood flow in the baboon *Circ Res* 25 77 1969
8 Strandgaard S Olsen J Skinhoj E and Lassen N A Autoregulation of brain circulation in severe arterial hypertension Br Med J 1 507 1973
9 Ponte J and Purves M J The role of the carotid body chemoreceptors and carotid sinus baroreceptors in the control of cerebral blood vessels, J Physiol (Lond) 237 315 1974
10 James I M and MacDonell L A The role of baroreceptors and chemoreceptors in the regulation of the cerebral circulation Clin Sci Mol Med 49 465 1975

)f cardiac output and congestive heart failure

It is generally accepted and taught that the clini al and athophysiologic manifestations of congestive heart failure CHF) are due to low cardiac output (C O) and that these manifestations disappear when cardiac output is increased This may be so but a reduction in C O cannot be the ole actor To rationalize the concept that low cardiac output is responsible for the clinical manifestations of CHF in instances when the cardiac output actually is high the terms high" and low cardiac output types of CHF were introduced Yet it is well known that the C O of normal man can be either extremely high or low but CHF is absent Compare the C O of normal man runnin 100 meters with that at 3 00 A M when he is in a deep sleep Furthermore when the manifestations of CHF are present these manifestati ons are similar regardless of the magnitude of C O at rest Exercise in a patient with CHF may increase cardiac output but th CHF worsens it d es not improve This situation is again rationalized by stating that even though the C O increased the increased needs for blood produced by the exer ise exceeded the C O so that the state of CHF worsened Again this may be so but is it? Furthermore a patient with CHF placed in a hot and humid environment has an incr ase in C O even at rest yet his state of CHF worsens The metabolic needs for blood are not increased to the degree of the increase in circulatory dynamics In spite of the increase in C O produced by the hot and humid environment the pathophysiologic state of CHF is extremely worsened. It does not improve

There is no doubt that the clini al state of chronic CHF originates in the heart but the mechanisms of the pathophysi ology remain to be explained and the role of cardiac output itself alone needs careful consideration and analysis The role of the central and autonomic nervous systems in CHF needs investigation Finally even though the mechanism of the pathophysiology of the clinical state of CHF is not well understood when therapy is properly and elegantly instituted and compliance is religiously obtained the therapeuti response is astonishingly favorable

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REFERENCES

1 Burch G E Influence of a hot and humid environment on the patient with coronary heart disease J Chronic Dis 4 350 1956
2 Burch, G E and Miller G C The effects of warm humid environment on patients with congestive heart failure South Med J 62 816 1969

Letters to the Editor

Effectiveness of direct current defibrillation role of paddle electrode size II

To the Editor

Previous studies from this laboratory have shown that defibrillator paddle electrodes with a diameter of 12 8 centimeters (cm) were more effective than those of 8 0 centimeters in defibrillating dogs who were allowed to remain in ventricular fibrillation for 15 to 60 seconds prior to defibrillatory attempts The reason for the increased effectiveness of the larger diameter paddle electrode may relate to the decrease in the transthoracic impedance that occurs with increasing paddle electrode size The transthoracic impedance encountered with 12 8 cm electrodes was 45 ± 7 ohms compared to 67 ± 10 ohms with the 8 0 cm electrodes When the same amount of energy is discharged from a direct current (DC) defibrillator into varying impedance loads the delivered peak current increases with decrea ing impedance Since it has been shown that a minimal current per body weight is necessary for transthoracic ventricular defibrillation in subjects weighing from 2 3 to 340 kilograms lowering the transthoracic impedance to direct current discharge should enhance defibrillation effectiveness

Since the transthoracic impedance to DC defibrillator discharge decreases with increasing electrode size defibrillator paddle electrodes larger than 12 8 cm in diameter might be even more effective because of further decreases in transthoracic apparent impedance On the other hand larger electrodes might be less effective because of a decreased current density with very large paddle electrode size

To test these postulates defibrillation effectiveness of defibrillator paddle electrodes that were 13 cm by 20 cm was tested and compared with the results obtained in our previous study with 12 8 cm diameter and 8 0 cm diameter electrodes Fifteen mongrel dogs ranging in weight from 18 4 to 26 4 kilograms (mean 21 6 kilograms) were anesthetized with pentobarbital 25 mg per kilogram given intravenously The thoracic hair was removed with electric clippers and the chest was shaved An endotracheal tube was inserted and the animals were ventilated with room air with a Harvard respirator A number four French bipolar electrode catheter was inserted into the right femoral vein and advanced into the right ventricle utilizing intracardiac electrocardiographic monitoring Ventricular fibrillation was induced by passing a 60 Hz current between the two poles of the electrode catheter until ventricular fibrillation was induced This required anywhere from 1 to 4 seconds

Defibrillation countershocks were delivered by a commercial direct current (DC) defibrillator that delivers a Lown waveform (Hewlett Packard defibrillator model 7802 C) The defibrillator meter setting was at 50 watt seconds The transthoracic apparent impedance was measured with each countershock by methods previously reported Redux paste (Hewlett Packard part No Col 1008 1) was used in liberal amounts on the paddle surface as paddle electrode chest wall interface The defibrillator paddle electrodes were held firmly on opposing lateral aspects of the dog s thorax at the level of the point of the maximal cardiac impulse

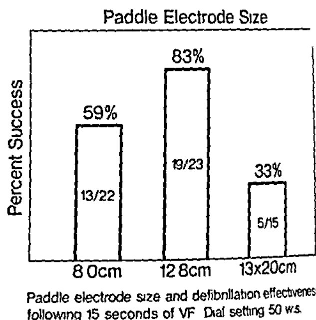


Fig 1 Relative defibrillation effectiveness of three different paddle electrode sizes

The single defibrillatory countershock attempt was given after the animal was in ventricular fibrillation for 15 seconds The criterion for a successful trial was defibrillation with restoration of an effective cardiac rhythm

The defibrillator success rate with the 13 by 20 cm paddle electrode was five out of fifteen or 33 per cent The mean transthoracic apparent impedance was 38 6 ohms There was no significant difference between the apparent impedance of the animals who were successfully defibrillated and those who were not (39 4 versus 38 3 ohms) nor was there any significant difference between the weight of the two groups (22 6 versus 21 1 kilograms) At the encountered impedance the mean delivered energy of each DC discharge calculated 27 ± 1 watt seconds

Observations on the effectiveness of the 8 0 cm diameter and 12 8 cm diameter paddle electrodes under the same experimental conditions as in this study reveal that the 8 cm paddle electrodes were effective at 59 per cent (13/22) and the 12 8 cm paddle electrodes were effective at 83 per cent (19/23) The larger size paddle electrodes i e 13 cm by 20 cm appear to be less effective 33 per cent (5/15) than are the 12 8 cm diameter paddle electrodes ($p < 01$) These relationships are shown in Fig 1

Transthoracic impedance to DC defibrillator discharge is dependent upon a number of parameters These include (1) energy level of the discharge (2) paddle electrode size (3) electrode-chest wall interface (4) whether or not the subject had received previous transthoracic DC countershocks and (5) the time interval between discharges In this and our previous study on the role of paddle electrode size and defibrillation effectiveness each of these parameters were constant except paddle electrode size Since previous defibrillation attempts alters transthoracic impedance these studies were done with only one transthoracic countershock in animals who had never been defibrillated before

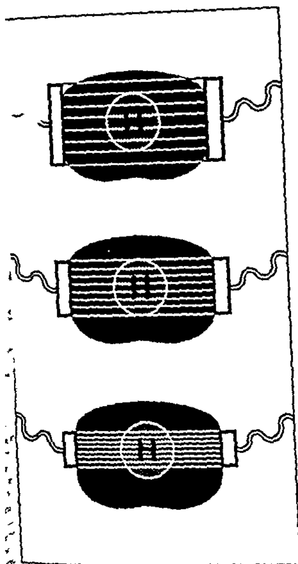


Fig 2 Diagrammatic representation of the relationship of current density (*represented by horizontal lines*) heart size (*H*) and paddle electrode size It illustrates the decreasing current density delivered to the heart with excessively large paddle electrodes. The pattern of current flow through the thorax is probably much like that of magnetic fields between two magnets and is *not* parallel as illustrated.

Table I shows the relationship between electrode size electrode area, transthoracic impedance delivered energy delivered peak current delivered current per centimeter squared electrode size defibrillation effectiveness, and mean weight of the animals. It can be seen that defibrillation effectiveness does not directly relate to any one of these single parameters.

Defibrillation effectiveness probably relates to the current density delivered to the heart *If* the current field is smaller than the cross-sectional area of the heart a critical mass of myocardium may not be depolarized and therefore the heart not be defibrillated At the other extreme if the electrode area becomes excessive then the current density delivered to the heart is inadequate for defibrillation These theoretical

Table I Defibrillation effectiveness Role of paddle electrode size

Electrode diameter (each)	*8 0 cm*	*12 8 cm*	*13 × 20 cm*
Electrode area (each)	*50.2 cm*	*129 7 cm*	*260 cm*
Thoracic impedance (ohms)	57 ± 11 Ω	47 ± 7 Ω	39 ± 9 Ω
Delivered energy (watt seconds)	33 ± 2	29 ± 1	27 ± 1
Delivered current (amps)	13 8 ± 1 2	16.0 ± 0 7	16 f ± 0 9
Delivered peak current per cm electrode area (single paddle)	0 275 amps / cm	0.124 amps / cm	0 064 amps / cm
Defibrillation effectiveness	59% 13/22	83% 19 23	33% 5/15
Mean weight of animals	21 5 kg	20 6 kg	21 6 kg

considerations are graphically illustrated in Fig 2 The drawings in Fig 2 are for illustration purposes only since the lines of current between defibrillator paddle electrode are *not* straight

Research is needed to determine the optimal electrode size in human size animals, and thus in humans.

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REFERENCES

1 Thomas E D Ewy G A Dahl C F and Ewy M D Effectiveness of direct current defibrillation Role of paddle electrode size Am Heart J 93 463 1977
2 Conn II I M Ewy G A Dahl C F et al Transthoracic impedance to defibrillation discharge Effect of electrode size and electrode-chest wall interface J Electrocardiol 6 313 19 3
3 Ewy G A Fletcher R D and Ewy M D Comparative analysis of direct current defibrillators J Electrocardiol 5 349 1972
4 Geddes L A Tacker W A Rosborough J et al Electrical dose for ventricular defibrillation of large and small animals using precardial electrodes J Clin Invest 53 310 1974
5 Ewy G A Ewy M D Nuttall A J and Nuttall A W Canine transthoracic resistance J Appl Physiol 32 91 1972
6 Dahl C F Ewy G A Ewy M D and Thomas F D Transthoracic impedance to direct current discharge effect of repeated countershocks Med Instrumentation (in press)
7 Zipes D P Fisher J King R M Nicoll A and Jolly W W Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium Am J Cardiol 36 37 19 5

Effectiveness of direct current defibrillation role of paddle electrode size II

To the Editor

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Since the transthoracic impedance to DC defibrillator discharge decreases with increasing electrode size defibrillator paddle electrodes larger than 12 8 cm in diameter might be even more effective because of further decreases in transthoracic apparent impedance On the other hand larger electrodes might be less effective because of a decreased current density with very large paddle electrode size

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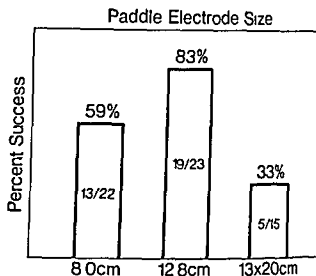


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Beta Blockers—Present Status and Future Prospects Edited by W. Schweizer Baltimore 1974 University Park Press. 3... pages. $19.50

This publication contains the papers presented at the International symposium at Juan les Pins May 27 to 29 1974 with all the proceedings of symposia selected aspects of the subject were discussed by selected investigators and clinicians from various parts of the world. Among the problems presented were the antihypertensive effects and actions and use of beta blockers, the effects of these agents on hemodynamic phenomena, use of these drugs in the United Kingdom, use of the drugs for cardiac arrhythmias, angina pectoris, myocardial ischemia, hypertrophic cardiomyopathy and thermal regulation. As usual the discussions are most interesting. The various reports are good including the attempts to explain the mechanisms of action of beta blockers in view of limited knowledge concerning the drugs and the circulation and the relative crudeness of most of the methods employed for the physiologic studies. Readers will find the book to be interesting and worth study especially if they use beta blockers in clinical practice. The papers and discussions reveal the differences in opinions and gaps in knowledge concerning the action and clinical use of these drugs.

British Medical Bulletin Immunological Tolerance (Vol 32 No 1 May 1976) Published by the Medical Department The British Council 65 Davies St London W1Y 2AA England.

In the usual tradition over several decades the *British Medical Bulletin* has contained important excellent and timely papers on important subjects in medicine. This is still true for this issue on immunological tolerance. This series of papers should interest surgeons physicians and immunologists who are particularly involved in the field of transplantation. Tissue typing tissue rejection and autoimmunity are among the subjects discussed. The contributors are well known in the field of tissue immunology and transplantation. This is an important review of important aspects of immunology. The issue is worth owning and studying.

Advances in Experimental Medicine and Biology Vol 67 Atherosclerosis Drug Discovery Edited by Charles E Day New York and London 1976 Plenum Press 467 pages

This volume of *Advances in experimental medicine and biology* has an interesting title in that the reader would expect to find at least one drug that can prevent or cure arteriosclerosis. But not even a drug for prevention has been discovered. The usual types of discussions of drugs and agents which influence blood lipids are presented along with discussions of newer ones. However atherosclerosis remains a major cause of death in man especially in old people. The many papers presented at the symposium held at the Brook Lodge in Augusta Mich. Aug 13 to 15 1975 are concerned mainly with fundamental studies on experimental models—primates birds, rabbits, rodents, and tissue culture. The papers are extremely interesting and basic in nature. They should interest biochemists, pathologists, physiologists, and pharmacologists. But clinicians will find the papers interesting but of little importance to the care of patients. These reports on animal experiments readily reflect the difficulties related to research in arteriosclerosis and cholesterol and lipoprotein metabolism. This is an important and interesting volume. These proceedings provide an opportunity for those who were not present at the symposium to learn of the presentations. This is a good publication.

Fundamentals of Vascular Radiology By Robert I White Jr M.D. Philadelphia 1976 Lea & Febiger Publishers 151 pages $1... 00

Dr White has written a book of about 150 pages on an important and complex subject in radiology for beginners. This book is different in that White describes his own experiences and includes a few important tricks he has learned to improve the technique and effectiveness of radiologic study of the large vessels of the body. The 1.. chapters are concerned primarily with techniques for diagnostic study of the heart and large vessels. The chapters include venography intestinal renal cerebral and pulmonary angiography and pediatric angiography. Apparatus instruments catheters radiopaque material techniques and interpretations are among the subjects presented. The references are well selected and the illustrations are very good. This is an excellent book especially for beginners in radiologic study of the vascular systems. Even experienced radiologists vascular surgeons and cardiologists will find the book worth owning.

Books received

Vascular Surgery A Guide and Handbook By Gerald H Pratt M.D. F.A.C.S. St Louis 1976 Warren H Green Inc 287 pages

Lipoprotein Metabolism Edited by Heiner Greten New York 1976 Springer Verlag Inc 15. pages

Drug Treatment Principles and Practice of Clinical Pharmacology and Therapeutics Edited by Graeme S Avery Acton Mass 1976 Publishing Sciences Group Inc 1048 pages Price $25.00

Coronary Angiography and Angina Pectoris Edited by P Lichtlen Acton Mass 1976 Publishing Sciences Group Inc 400 pages Price $26.00

Short preceptorships for postgraduate training in new techniques

To the Editor

A major failing of postgraduate medical education is that there is very little opportunity for a physician to learn *new techniques* in a *short formal teaching program* once he has finished his fellowship There are abundant seminars medical meetings cassette tape transcriptions of lectures and other such modalities for teaching theoretical concepts However the academic community has not provided satisfactory ways for the physician or surgeon to learn new techniques For example in the past 15 years in Cardiology alone *Echocardiography Exercise stress electrocardiography Swan Ganz catheterization* the passage of an *emergency transvenous pacemaker His electrography* the rendering of the entire spectrum of *critical care medicine in a coronary care unit DC defibrillation Holter monitoring* the emergency introduction of an *intra aortic balloon* for cardiogenic shock *etc* all have become important techniques in the practice of Cardiology Yet even for those of us connected with a university teaching center gaining actual experience in these techniques is difficult For the majority of physicians not so academically connected the problem is compounded a hundredfold

Surgeons have similar difficulties in learning new operative procedures and because of the nature of their work this defect in their postgraduate education is even more serious than in the case of internists and pediatricians Those surgeons that I have questioned confide that if they are to gain such experience in new techniques at all they do so by surreptitiously scrubbing in with a friend who is adept at performing the new procedure or if this is not possible by simply trying out the procedures *de novo* on their own patients For example almost all present day colonoscopists are self trained they simply buy the instrument and try it out on their patients Cardiac surgeons who graduated as recently as 10 years ago have learned the new techniques of coronary venous bypass surgery by similar dubious methods Established orthopedic surgeons implant prosthetic knees and hips with knowledge gained by reading about the techniques in a journal or by the see one—do one method Obviously such solutions are ethically unacceptable and have explosive potential for medico legal disaster particularly in the present litigious climate of society

My suggestion for a more satisfactory solution to this problem is a series of *full time 1 to 4 week Preceptorships* at a major medical center The physician or surgeon would work full time at the institution during this period a time interval that most physicians or surgeons could afford to take off from their practices or university positions For the more commonly performed new techniques the physician or surgeon should be able to acquire a reasonable amount of expertise within this period of time particularly if the university hospitals make it a point of concentrating their elective cases involving this procedure within this teaching interval For the less common procedures or for the procedures done only randomly at the time of an emergency a student specialist might have to return for a repetition of the course two or three times over a period of a year or two to gain adequate expertise With *adequate record keeping* of the student s progress such *cumulative experience could be had in different institutions at the* student s convenience

I would also recommend that each teaching department apply to the appropriate certifying organization—American College of Cardiology American College of Surgeons, etc—for official approval of these courses and that after the successful completion of these courses an *officially stamped certificate diploma* be given to the candidate This would carry great weight not only in a court of law but with the administrations of the community hospital where the physician or surgeon may want to introduce the new procedure

I predict that the introduction of such a program would elicit an enormously popular response from all over the country

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TAPVC vital statistics Ethics and moral values

To the Editor

It is obvious that Dr Bharati s article[1] is the largest series of TAPVC S dealing only with morbid pathological anatomy and Dr Van Praagh s excellent review[2] is the largest series of diagnostic and surgical aspects of TAPVC

The point I would like to make is that a research trainee need not feel frustrated if her (or his) work is not included or quoted in the bibliography It is entirely up to the author s discretion individual judgment and free decision to quote and select reference articles of inherent worth and intrinsic value pertaining to his subject matter It is his prerogative to separate the chaff from the grain *And* this is the basic to all aspects of scientific publications

A research trainee need not expect other workers to be all embracing in choosing references and bibliography The day of the learned review is almost over The year books which exist in almost every subject now subserve this function In general the best original papers have the fewest references

Internal anxiety about non recognition of one s own work should not be projected and distorted as a phoney concern about a chance reader getting erroneous ideas

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REFERENCES

1 Bharati S and Lev M Congenital anomalies of the pulmonary veins Cardiovasc Clin 5 23 1973
2 Delisle G Ando M Calder A L Zuberbuhler J R Rochenmacher S Alday L E Mangini O Van Praagh S and Van Praagh R Total anomalous pulmonary venous *connection* Report of 93 autopsied cases with emphasis on diagnostic and surgical considerations Am Heart J 91 99 1976
3 Bharati Saroja TAPVC vital statistics (Letter to Editor) Am Heart J 92 410 1976
4 Van Praagh R Reply (Letter to Editor) Am Heart J 92 410 1976

American Heart Journal

June 1977 Volume 93 Number 6

ditorial

lagnesium and the heart

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It is well established that potassium is important for the functioning of the heart The role of other metal ions is less well known and in particular magnesium probably deserves more attention than it is usually given This is surprising as it was the medicinal properties of magnesium sulphate which first led chemists to recognize the existence of the element magnesium In 1695 Dr Nehemiah Grew examined the bitter mineral water from wells at Epsom Surrey and prepared solid magnesium sulphate which was popularly christened Epsom salts The element magnesium was not isolated until 1808 when the English chemist Sir Humphrey Davy prepared it from magnesium oxide Magnesium salts were shown to be con tituents of plants in the eighteenth century but the importance of magnesium salts in animals has only been demonstrated in this century

Biochemistry of magnesium

Magnesium is very important as an activator of many enzymes particularly all those concerned with the metabolism of adenosine triphosphate (ATP) *In vitro* manganese can usually replace magnesium in activating these enzymes but tissues generally contain much less manganese than magnesium It has been suggested that a magnesium ATP complex is the true substrate for all reactions involving ATP

In heart tissue magnesium has been shown to be involved in ATP hydrolysis by myofibrils superprecipitation and syneresis of actomyosin gels and binding and release of calcium by sarco tubules—reactions which are all essential to the contraction of heart muscle Magnesium also stimulates oxidative phosphorylation in heart mitochondria affects the sodium-potassium ATPase of heart membranes and activates adenyl cyclase (and probably phosphoryla e kinase) in the heart[2]

Magnesium in animal hearts

Studies of heart disease in experimental animals are not necessarily directly applicable to human problems but they often provide useful information There is a great deal of evidence that magnesium is involved in heart disease in animals and this has been reviewed recently[1,3] Many studies have shown that there is a rapid loss of magnesium from the heart when it is made anoxic experimentally Potassium concentrations in the anoxic heart also decrease but the magnesium decrease usually precedes the potassium loss Magnesium deficient diets often produce changes in heart metabolism in animals and predispose animals to the development of myocardial fiber necrosis

Administration of magnesium salts has been shown to reverse many of the changes in animal models of heart disease There is also good evidence from some animal studies that pre

From the Departments of Biochemistry and Chemistry Un ersity of H ll, Hull, England

Rece ved f publ at n Oct 5 19 6

Reprint requests D B Chipperfi ld Dept. of B ochemistry Un e sity f Hull, Hu HU6 7RX England.

Announcements

American Board of Internal Medicine Guidelines for Training in Cardiovascular Disease

In response to requests for its opinion concerning excellent subspecialty training programs the American Board of Internal Medicine has prepared guidelines for training in the subspecialties of internal medicine Since subspecialists devote considerable professional time and effort to general internal medicine and must also be trained to conduct this aspect of their practices with competence the Board has also prepared statements on the Attributes of the General Internist as well as the Attributes of the Subspecialist in Internal Medicine to be distributed with its Guidelines for Training in Cardiovascular Disease

The Board emphasizes that these documents should be received as recommendations offered in response to requests for assistance and not as requirements to be enforced through the Boards certification process This material can be obtained by directing a written request to The American Board of Internal Medicine 200 S W Market St Portland Oregon 97201

Nurse Clinician Series seminar

A Nurse Clinician Series seminar entitled Acid base blood gases and electrolyte disorders will be held at the Sheraton Sand Key Hotel Clearwater Beach Florida on June 16 through 18 1977 The seminar will be directed by David P Lauler M D Chief of Medicine at the Lawrence and Memorial Hospitals New London Connecticut For further information regarding the seminar please contact Ms Billie Chiles Tampa Tracings P O Box 1245 Tarpon Springs FL 33589

International Conference on Atherosclerosis

An International Conference on Atherosclerosis sponsored by the European Group for the Study of Atherosclerosis and the Italian Society for Atherosclerosis Research is being organized by the Lorenzini Foundation of Milano The Congress will take place in Milan Italy on November 9 through 11 1977 and will be divided into the following sessions (1) Atherosclerosis and Heart (2) Atherosclerosis and Brain (3) Atherosclerosis and Peripheral Circulation Round tables are planned on primary and secondary prevention new analogs of clofibrate lipoprotein metabolism platelet antiaggregants dietary prevention of atherosclerosis mucopolysaccharides phospholipids new antiatherosclerotic agents.

Chairmen of the meeting are L Carlsson Stockholm R Paoletti Milano and G Weber Siena A limited number of free communications shall be accepted All correspondence and requests for information should be sent to Fondazione G Lorenzini Via Montenapoleone 23 Milano Italy Tel (02) 783868

International Symposium on bypass grafting

The Cleveland Clinic Foundation announces an International Symposium entitled "The First Decade of Bypass Graft Surgery for Coronary Artery Disease to be held on September 15 16 and 17 1977 in Cleveland Ohio

Information may be obtained by contacting the Director of Continuing Medical Education The Cleveland Clinic Foundation 9500 Euclid Ave Cleveland Ohio 44106 Tel 216-444-5696

Society of Nuclear Medicine meeting

The second Annual Western Regional Meeting of the Society of Nuclear Medicine will be held at the Aladdin Hotel in Las Vegas Nevada October 21 22 and 23 1977 The Northern California Southern California Pacific Northwest, and Hawaii Chapters are sponsoring this meeting The program will consist of invited papers contributed papers registry review courses for technologists and refresher courses for physicians The Scientific Program Committee is encouraging the submission of scientific exhibits in addition to contributed papers The deadline for submission of abstracts is July 8 1977 The deadline for submission of scientific exhibits is August 1 1977 Support and interest from commercial companies is invited We anticipate an outstanding commercial exhibits display

Please address all correspondence regarding the submission of abstracts and the exhibiting of commercial companies to Justine J Lynch Administrative Coordinator P O Box 40 [illegible] San Francisco CA 94140 Telephone (415) 647 0 [illegible] or 64 5909

with magnesium salts after myocardial infarction may increase survival and relieve pain Better trials of this treatment are needed

Dietary magnesium and prevention of heart disease

Since reduction of magnesium seems to be associated particularly with sudden death from ischemic heart disease[1] attention should perhaps be given to the dietary content of magnesium in the prevention of death from heart disease Seelig[3] estimates that although the Oriental diet provides 6 to 10 mg of magnesium per Kg the average American or British diet provides less than 5 mg of magnesium per Kg This dietary intake will not be sufficient to keep normal males in magnesium balance[3] though Schroeder and colleagues[15] consider that the magnesium balance studies demonstrating this effect are unreliable This is a problem which should be re investigated using more accurate modern methods of estimation of magnesium

Reviews of the magnesium content of food stuffs[3] show that meat and fish (particularly shellfish) green vegetables peas beans and most fruits are rich in magnesium Fats refined flour white sugar and spirits are very low in magnesium Choice of diet can therefore make a big difference to the daily intake of magnesium Perhaps the increased incidence of heart disease in Scotland compared with England is due to the English drinking beer which contains about twenty times as much magnesium as the whisky drunk by the Scots

Patients who avoid fats and refined carbohydrates and increase their intake of meat fish fruit and vegetables will increase their daily intake of magnesium and other mineral salts which might well affect the functioning of the heart We have not been able to find any studies which indicate that magnesium intake in the diet affects the incidence of heart disease or the course of established heart disease but this subject is probably worth investigation

Conclusions

There is now considerable evidence that myocardial infarction leads to a loss of magnesium from the heart muscle and that a low heart muscle magnesium may contribute to sudden death after myocardial infarction Western diets are probably often low in magnesium so that the magnesium in hard drinking water may help to protect its consumers from ischemic heart disease

Increasing the magnesium content of the diet may help to prevent ischemic heart disease and there is already evidence that magnesium salts can have beneficial effects on established heart disease Both aspects of magnesium and the heart deserve further investigation

REFERENCES

1 Szent Györgyi, A The ATP molecule Bioenergetics, New York, 1957 Academic Press, Inc p 64
2 Polimeni, P I and Page E Magnesium in heart muscle Circ Res. 33 367 1973.
3 Seelig M S Myocardial loss of functional magnesium II in cardiomyopathies of diverse etiology Recent Advan Stud Cardiac Struct. Metabol. 1 626 1972.
4 Seelig M S and Heggtveit H A Magnesium interrelationships in ischemic heart disease Am J Clin Nutr 27 59 1974
5 Wüstenberg, P W Der Magnesiumstoffwechsel aus kardioangiologischer Sicht I Befunde des Magnesiumhaushaltes bei Herzerkrankungen Z. Gesamte Inn Med 27 45 1972
6 Lehr D Chau R., and Irene S Possible role of magnesium loss in the pathogenesis of myocardial fiber necrosis, Recent Advan. Stud. Cardiac Struct. Metabol 6 95 1975
7 Urbánek, E., Vašků J Bednařík B Prasbička M., and Pospíšil M Electrolyte changes in myocardial injury Recent Advan Stud Cardiac Struct. Metabol. 6 43, 1975
8 Fedelešová M Ziegelhöffer A Luknárová O., and Kostolanský Š Prevention by K Mg aspartate of isoproterenol induced metabolic changes in the myocardium Recent Advan Stud. Cardiac Struct. Metabol. 6 59 1975
9 Janke J Fleckenstein A Hein B Leder O., and Sigel H Prevention of myocardial Ca overload and necrotization by Mg and K salts or acidosis, Recent Advan Stud Cardiac Struct Metabol. 6 33 1975
10 Chipperfield B and Chipperfield J R. Heart muscle magnesium potassium and zinc concentrations after sudden death from heart-disease Lancet 2 293 1973
11 Behr G and Burton P Heart muscle magnesium Lancet 2 450, 1973
12 Chipperfield B and Chipperfield J R. Unpublished results
13 Crawford M D Gardner M J., and Morris J N Cardiovascular disease and the mineral content of drinking water Br Med Bull. 27 1 1971
14 Anderson T W Le Riche W H and MacKay J S Sudden death and ischemic heart disease Correlation with hardness of local water supply N Engl J Med 280 805 1969
15 Schroeder H A., Nason A P and Tipton I H Essential metals in man magnesium J Chronic Dis 21 815 1968
16 Anderson T W Neri, L C Schreiber G B Talbot, F D F and Zdrojewski A. Ischemic heart disease water hardness and myocardial magnesium Can Med Assoc J 113 199 1975
17 Chipperfield B., Chipperfield J R., Behr G., and Burton P Magnesium and potassium content of normal

treatment with magnesium salts protects against many of the changes in the heart caused by anoxia[4] and can also protect against myocardial necrosis induced by drugs [4, 9]

Magnesium and human ischemic heart disease

A number of investigations have shown that the concentration of magnesium in human heart muscle is decreased after death from myocardial infarction [3, 4] This lower magnesium concentration is found both in infarcted muscle and also in areas which are not infarcted and which show normal potassium concentrations [10] There is no decrease in the magnesium concentration in skeletal muscle accompanying the cardiac muscle decrease, and the heart muscle of patients dying from chronic heart disease does not show this decreased magnesium concentration [11, 1] This suggests that patients who have lower than normal magnesium concentrations in their heart muscle would be more likely to die suddenly after a myocardial infarction

The association of low heart muscle magnesium with sudden death from ischemic heart disease, but not with death following chronic heart illness is interesting in relation to the well established[1] increased death rate from heart disease in areas with soft drinking water Anderson and co workers[1] have shown that the increased death rate in soft water areas is due entirely to an excess of sudden deaths rather than deaths from chronic disease and several reviewers have discussed the theory that it is lack of magnesium in soft drinking water which is the important factor in the soft water story [1, 4, 11, 1]

Anderson s group[1] has now shown that heart muscle from people dying after accidents in soft water areas of Ontario had a significantly lower concentration of magnesium than similar samples from inhabitants of hard water areas We found[1] that normal heart muscle from inhabitants of soft water areas had somewhat higher concentrations of magnesium but that the magnesium/potassium ratio was lower when compared with normal heart muscle from people from a hard water area The difference in the magnesium concentrations of the hard and soft water in England was much smaller than that found in Canada, but there was still an increased death rate from heart disease in the soft water areas

Seelig[18] has reviewed studies of human dietary magnesium balance and found that the low magnesium content of Western diets would lead to a small deficit of magnesium in men but not in women This correlates well with the higher incidence of ischemic heart disease in men. Schroeder and colleagues[15] have dismissed these studies as most of the work was carried out before the recent improvment of methods for estimation of magnesium It is perhaps relevant that we have recently shown[1] that normal men have a significantly lower concentration of magnesium in their heart muscle than women which again fits in well with the higher incidence of male ischemic heart disease

Patients who are deficient in magnesium as a result of protein calorie malnutrition[1] or alcoholic heart disease show marked electrocardiographic changes, and these are also found when human magnesium deficiency has been experimentally induced [1] There is also good evidence that diuretics can cause magnesium deficiency which makes the heart susceptible to the development of arrhythmias particularly during digitalis therapy [5]

Magnesium therapy for heart disease

Flink [6] has reviewed the treatment of magnesium deficiency He considers that magnesium sulphate chloride or acetate are all equally effective, whether given intravenously (if the patient is having an intravenous infusion) or intramuscularly Oral therapy is more difficult to control, and much magnesium given orally is not absorbed [27] Tansy has reviewed the evidence on intestinal absorption of magnesium salts Magnesium absorption from the gut may be affected by calcium and vitamin D given at the same time [18, 4]

Magnesium compounds have been used successfully in the treatment of arrhythmias associated with digitalis therapy [1] A number of reports, particularly from European countries have shown subjective and objective improvements in patients with ischemic heart disease treated with magnesium salts and these reports are well reviewed by *Seelig and Heggtveit*[4] and Wustenberg[3] Magnesium aspartate has been given most commonly but the sulphate nicotinate thiosulphate, adipinate and levulinate have also been employed Few of the studies have been good controlled clinical trials and many of them have combined several forms of therapy There is however considerable evidence that treatment

ith magnesium salts after myocardial infarction may increase survival and relieve pain Better trials of this treatment are needed

Dietary magnesium and prevention of heart disease

Since reduction of magnesium seems to be associated particularly with sudden death from ischemic heart disease[1] attention should perhaps be given to the dietary content of magnesium in the prevention of death from heart disease Seelig estimates that although the Oriental diet provides 6 to 10 mg of magnesium per Kg the average American or British diet provides less than 5 mg of magnesium per Kg This dietary intake will not be sufficient to keep normal males in magnesium balance[1] though Schroeder and colleagues[5] consider that the magnesium balance studies demonstrating this effect are unreliable This is a problem which should be re investigated using more accurate modern methods of estimation of magnesium

Reviews of the magnesium content of food stuffs [5] show that meat and fish (particularly shellfish) green vegetables peas beans and most fruits are rich in magnesium Fats refined flour white sugar and spirits are very low in magnesium Choice of diet can therefore make a big difference to the daily intake of magnesium Perhaps the increased incidence of heart disease in Scotland compared with England is due to the English drinking beer which contains about twenty times as much magnesium as the whisky drunk by the Scots

Patients who avoid fats and refined carbohydrates and increase their intake of meat fish fruit and vegetables will increase their daily intake of magnesium and other mineral salts which might well affect the functioning of the heart We have not been able to find any studies which indicate that magnesium intake in the diet affects the incidence of heart disease or the course of established heart disease but this subject is probably worth investigation

Conclusions

There is now considerable evidence that myocardial infarction leads to a loss of magnesium from the heart muscle and that a low heart muscle magnesium may contribute to sudden death after myocardial infarction Western diets are probably often low in magnesium so that the magnesium in hard drinking water may help to protect its consumers from ischemic heart disease

Increasing the magnesium content of the diet may help to prevent ischemic heart disease and there is already evidence that magnesium salts can have beneficial effects on established heart disease Both aspects of magnesium and the heart deserve further investigation

REFERENCES

1 Szent Györgyi, A The ATP molecule Bioenergetics, New York 1957 Academic Press Inc. p 64
2 Polimeni P I and Page E Magnesium in heart muscle Circ Res. 33 367 1973
3 Seelig M S Myocardial loss of functional magnesium II in cardiomyopathies of diverse etiology Recent Advan. Stud. Cardiac Struct. Metabol 1 676 1972
4 Seelig M S and Heggtveit H A Magnesium interrelationships in ischemic heart disease Am J Clin Nutr 27 59 1974
5 Wüstenberg P W Der Magnesiumstoffwechsel aus kardioangiologischer Sicht I Befunde des Magnesium haushaltes bei Herzerkrankungen Z Gesamte Inn Med 27 45 1972
6 Lehr D Chau R., and Irene S Possible role of magnesium loss in the pathogenesis of myocardial fiber necrosis Recent Advan Stud. Cardiac Struct. Metabol 6 95 1975
7 Urbánek, E., Vaškū J Bednařík B Prasličká M and Pospíšil M Electrolyte changes in myocardial injury Recent Advan Stud Cardiac Struct Metabol. 6 43 1975
8 Fedelešová M Ziegelhöffer A., Luknárová O and Kostolansky Š Prevention by K Mg aspartate of isoproterenol induced metabolic changes in the myocardium Recent Advan Stud Cardiac Struct. Metabol 6 59 1975
9 Janke J Fleckenstein A Hein B Leder O., and Sig I H Prevention of myocardial Ca overload and necrotization by Mg and K salts or acidosis Recent Advan Stud Cardiac Struct Metabol. 6 33 1975
10 Chipperfield B and Chipperfield J R. Heart muscle magnesium potassium and zinc concentrations after sudden death from heart disease Lancet 2 293 1973
11 Behr G and Burton P Heart muscle magnesium Lancet 2 450 1973
12 Chipperfield B and Chipperfield J R Unpublished results.
13 Crawford M D Gardner M J., and Morris J N Cardiovascular disease and the mineral content of drinking water Br Med Bul 27 1 1971
14 Anderson T W Le Riche W H and MacKay J S Sudden death and ischemic heart disease Correlation with hardness of local water supply N Engl J Med 280 805 1969
15 Schroeder H A Nason A. P., and Tipton I H Essential metals in man magnesium J Chronic Dis 21 815 1968
16 Anderson T W Neri, L C Schreiber G B Talbot F D F and Zdrojewski A Ischemic heart disease water hardness and myocardial magnesium Can Med. Assoc J 113 199 1975
17 Chipperfield B Chipperfield, J R Behr G and Burton P Magnesium and potassium content of normal

heart muscle in areas of hard and soft water Lancet 1 121 1976
18 Seelig M S The requirement of magnesium by the normal adult Am J Clin Nutr 6 342 1964
19 Cadell J L Magnesium deficiency in protein calorie malnutrition Ann N Y Acad Sci 162 874 1969
20 Seelig M S Electrographic patterns of magnesium depletion appearing in alcoholic heart disease Ann N Y Acad Sci 162 906 1969
21 Shils M E Experimental production of magnesium deficiency in man Ann N Y Acad Sci 162 847 1969
22 Wacker W E and Parisi A F Magnesium metabolism N Engl J Med 278 772 1968
23 Seller R H The role of magnesium in digitalis toxicity Am Heart J 82 551 1971
24 Bloch M Magnesium depletion possible significance in ischemic heart disease British J of Hospital Medicine 9 91 1973
25 Lim P and Jacob E. Magnesium deficiency in patients on long term diuretic therapy for heart failure, Br Med J 3 620 1972
26 Flink E B Therapy of magnesium deficiency Ann N Y Acad Sci 162 901 1969
27 Aikawa J K The role of magnesium in biologic processes Springfield Ill 1963 Charles C Thomas, Publisher
28 Tansy M F Intestinal absorption of magnesium, p 193, *in* Intestinal absorption of metal ions, trace elements and radionuclides, ed Skoryna S C Oxford, 1971, Pergamon Press Inc
29 Schlettwein Gsell D and Mommsen Straub, S. Übersicht Spurenelemente in Lebensmitteln VII Magnesium, Int J Vitam Nutr Res. 42 324 1972.
30 McCance R A and Widdowson E M The composition of foods, M R C Special Report No 297 London, 1960 Her Majesty s Stationery Office

The prevalence of angina pectoris and abnormal coronary arteriograms in severe aortic valvular disease

Thomas B Graboys, M D
Peter F Cohn M D
Boston, Mass

Angina pectoris is thought to be more common in patients with severe aortic valve disease who have predominant aortic stenosis compared to those who have predominant aortic regurgitation[1,2] However there are very few reports comparing the frequency of angina in a large series of consecutively studied patients with severe aortic valve disease who have also undergone coronary arteriography to document associated coronary artery disease (CAD)

Methods

This study consists of 66 consecutive patients (42 male 24 female) with solitary aortic valve disease evaluated in the Cardiovascular Division of the Peter Bent Brigham Hospital Patients were selected because they fulfilled the criteria for significant aortic valve disease (CF) All subsequently underwent aortic valve replacement 10 of whom also had simultaneous coronary artery bypass graft surgery All patients underwent diagnostic right and left heart catheterization Diagnostic quality selective coronary cine arteriograms were obtained on 16 mm Ilford Pan F film with either GE or Siemens 6 inch or dual field x ray image intensification Stenosis of 75 per cent or greater of a coronary vessel lumen was considered significant

For purposes of this study three groups of patients were identified Patients in Group 1 had predominant aortic stenosis defined as a peak to peak transvalvular gradient of ≥ 40 mm Hg and/or a calculated aortic valve area of < 0 7 cm² with minimal (0 to 1 on a scale of 4) aortic regurgitation Patients in Group 2 had predominant aortic regurgitation defined by root aortography[3] as moderate to severe (3 to 4 on a scale of 4) with less than a 10 mm transvalvular gradient Patients in Group 3 had significant mixed disease defined as a transvalvular gradient of at least 40 mm Hg with concomitant (2 to 4 on a scale of 4) aortic regurgitation

Angina pectoris was defined as substernal or left precordial chest pain or pressure precipitated typically by exercise emotion stress or cold exposure and promptly relieved by rest or nitroglycerin[4] Angina pectoris was graded in severity as follows Class 1 or 2 precipitated by various degrees of extraordinary exertion Class 3 angina provoked by ordinary activities or by *cold or* emotional factors class 4 nocturnal or rest angina

Results

Fig 1 details data from the three study groups

Group 1 (predominant aortic stenosis) *Nine*teen patients (mean age 62 range 47 to 76 12 male 7 female) with a mean peak to peak aortic gradient of 92 mm Hg (range 40 to 128) were included in this *group Twelve* had angina pectoris, of whom four had significant CAD No patients without angina had significant CAD

Group 2 (predominant aortic regurgitation) Twenty nine patients (mean age 49 range 29 to 64 17 male 12 female) comprised this group Eighteen had angina pectoris of whom four demonstrated significant CAD One patient

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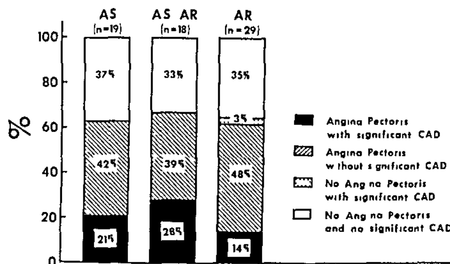


Fig 1 Prevalence of both angina pectoris and coronary artery disease (CAD) in patients with aortic stenosis (AS) and regurgitation (AR) There is no significant variation in any of the three subgroups

Table I Severity of angina pectoris and its relationship to coronary artery disease in patients with aortic valvular disease

	Grade angina pectoris		
	I II	*III*	*IV*
Total patients with angina pectoris (42)	17 (40%)	13 (31%)	12 (29%)
Patients with angina pectoris and associated CAD (13)	5 (38%)	5 (38%)	3 (24%)

Table II Site and extent of coronary artery disease in 14 patients with aortic valvular disease

Site	*No*
LAD*	6
LCF * LAD	3
RCA*	3
LCF LAD RCA	1
LCF	1

LAD left anterior descending LCF left circumflex RCA right coronary artery

without angina pectoris was found to have significant CAD—a 90 per cent lesion in the proximal right coronary artery in a balanced system

Group 3 (mixed aortic stenosis and regurgitation) Eighteen patients (mean age, 53 range, 40 to 69, 13 male, 5 female) with a mean peak to peak gradient of 55 mm Hg comprised this group Twelve were found to have angina pectoris five of whom demonstrated significant CAD Again in the nonanginal group no significant coronary atherosclerosis was found

Table I details the severity of angina pectoris Categorization of patients in Classes 1 to 4 was not helpful in predicting associated CAD

Table II outlines the anatomic location in the patients found to have coronary artery disease Fourteen patients were found to have significant CAD (average age 57) These were equally divided among the three subgroups Ten patients demonstrated single vessel disease three had two vessel, and one had three vessel disease There were no perioperative deaths in the 10 patients who underwent both aortic valve replacement and coronary artery bypass graft surgery, whereas one of the four patients who had aortic valve replacement only died Four additional patients had less than 50 per cent obstructive lesions, and underwent uncomplicated aortic valve replacement without coronary artery bypass surgery

Discussion

The prevalence of angina pectoris in patients with significant aortic valve disease has been reported to be between 40 to 80 per cent for predominant aortic stenosis [4] and 3 to 30 per cent for predominant aortic regurgitation [2] The mechanism of angina in aortic stenosis has been explained by a decreased myocardial oxygen supply due to both reduced coronary perfusion through a fixed stenotic valve orifice and prolonged left ventricular ejection time with a corresponding decrease in diastolic filling period as well as an increased myocardial oxygen

requirement because of increased wall tension (due to elevated left ventricular end diastolic pressure and thickness)[2,3] The basis of angina in aortic regurgitation also involves an imbalance between myocardial oxygen need and supply with both an increase in wall tension (due to elevated end-diastolic volume) as well as a lower than normal coronary perfusion pressure during diastole In both diseases associated CAD may also contribute to myocardial ischemia In the present study we found a high frequency of angina pectoris *throughout* the entire spectrum of severe aortic valve disease Although preselection of patients might account for the overall frequency of angina it would not explain the remarkably similar percentage in each of the three subgroups (*Fig 1*)

The frequency of associated CAD in the three sub groups varied only from 14 to 28 per cent for an over all average of 20 per cent indicating that in *most* cases angina was not due to associated CAD The prevalence of multivessel disease was low suggesting that patients with both extensive CAD *and* aortic valve disease are rare or do not survive long enough to be referred for catheterization Significant CAD without angina pectoris was infrequent (one patient) This finding raises the question of whether coronary arteriography is necessary in patients with aortic valve disease but without angina pectoris Authors disagree on this point

The prevalence of significant coronary artery disease defined by angiography in patients with aortic valve disease has varied in previous reports from between 20 to 63 per cent[1, 2] depending in part on the degree of luminal obstruction considered significant We do not consider less than 75 per cent narrowing significant since it is not associated with significant changes in coronary blood flow[7] Linhart and colleagues[8] recommended routine coronary angiography on all patients prior to aortic valve replacement based on a 48 per cent frequency of coronary artery disease in patients with aortic valve disease They also found that four of 16 patients with critical aortic stenosis without angina had severe CAD (75 per cent luminal obstruction) Hancock[4] found 56 per cent of 173 patients with aortic stenosis to have significant CAD Twelve of 45 (33 per cent) patients additionally had CAD (50 per cent luminal narrowing) in the absence of angina pectoris Moraski and co workers found a 46 per cent frequency of significant CAD (50 per cent vessel narrowing) in patients with aortic stenosis and a 9 per cent frequency of CAD in those patients without associated angina Harris and colleagues found 23 per cent of 69 patients with severe aortic stenosis to have significant CAD (75 per cent luminal stenosis) only three of whom had significant CAD without angina

In contrast to the above studies, our data are in agreement with those studies which contend that routine coronary angiography can probably be omitted in patients without angina pectoris especially those less than 65 Bonchek and associates[10] found a 10 per cent frequency of severe CAD in patients with aortic valve disease yet none of the 65 patients evaluated had significant CAD in the absence of angina Basta and co workers[2] found a 13 per cent frequency of significant (75 per cent luminal obstruction) CAD among a group of 88 patients with severe aortic valve disease but of 19 patients without angina pectoris who had aortic valve disease none had significant CAD Thirty one per cent of our patients with angina pectoris demonstrated significant CAD, yet only one patient without angina pectoris was found to have CAD as defined above and the nature of the lesion in a balanced coronary system invariably *would negate the need for* coronary artery bypass surgery in an otherwise asymptomatic individual

Does combined coronary artery bypass grafts and aortic valve replacement carry an additional operative mortality rate than aortic valve replacement alone? The numbers in the present study are too small for comparing aortic valve *replacement* alone to a combined procedure Randomly prospective studies may not be possible since at most institutions high grade obstructive lesions in either the left main or left anterior descending system are routinely being bypassed with concomitant aortic valve replacement

In conclusion this study has systematically examined the frequency of angina in the spectrum of severe aortic valvular disease and found it to be *essentially* the same in patients with aortic stenosis and regurgitation At present there is no question regarding the need for coronary angiography in patients with *angina* pectoris being evaluated for aortic valve disease since about 30

per cent of such patients will have CAD The decision to empirically perform this as a routine procedure, however, on all patients in the absence of a well defined chest pain syndrome is still subject to debate

Summary

In order to relate the frequency of angina pectoris to associated coronary artery disease, 66 consecutive patients with severe aortic valvular disease were studied by cardiac catheterization, including coronary angiography Angina pectoris was found in 63 per cent of patients with predominant aortic stenosis 62 per cent with aortic regurgitation, and 67 per cent with mixed disease Associated coronary artery disease (≳ 75 per cent luminal stenosis) ranged from 14 to 28 per cent and averaged 20 per cent for the entire group of 66 patients Only one patient without angina had significant coronary artery stenosis Our studies indicate that angina pectoris is equally common in all forms of severe aortic valve disease and is usually not associated with significant coronary artery disease

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REFERENCES

1 Friedberg C K Angina pectoris in Diseases of the heart ed 3 Philadelphia 1966 W B Saunders Company pp 706-715
2 Basta L L Raines D Najjar S et al Clinical haemodynamic and coronary angiographic correlates of angina pectoris in patients with severe aortic valve disease Br Heart J **37** 150 1975
3 Delany D J Aortography Cardiac catheterization and angiography W Grossman editor Philadelphia 1974, Lea & Febiger Publishers, p 150
4 Moraski R E Russell R O and Rackley C E Aortic stenosis, angina pectoris and coronary artery disease Circulation **49**(Suppl 3) 3 1974
5 Fallen E L Elliott W C and Gorlin R Mechanisms of angina in aortic stenosis Circulation **36** 480 1967
6 Linhart J W de la Torre A Ramsey H W et al The significance of coronary artery disease in aortic valve replacement J Thorac Cardiovasc Surg **55** 811 1968
7 Smith S C Gorlin R Herman M V et al Myocardial blood flow in man Effects of coronary collateral circulation and coronary artery bypass surgery J Clin Invest **51** 2556 1972
8 Hancock E W Clinical assessment of coronary artery disease in patients with aortic stenosis Am J Cardiol **35** 142 1975
9 Harris C N Kaplan M A Parker D P, et al Aortic stenosis, angina and coronary artery disease—interrelations Br Heart J **37** 656 1975
10 Bonchek L I Anderson R P and Rosch J Should coronary arteriography be performed routinely before valve replacement Am J Cardiol **31** 462 1973

Determinants of left ventricular function following aorto coronary bypass surgery

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There continues to be controversy over the effects of coronary artery bypass surgery on left ventricular function * Thirty patients were studied in order to evaluate ventricular function before and an average of 5 months after surgery The patients were grouped according to operative indications preoperative condition perioperative events and postoperative status in an effort to elucidate the determinates of postoperative function

Materials and methods

Thirty patients undergoing saphenous vein bypass grafting of the coronary arteries at Walter Reed Army Medical Center form the basis of this study The surgery was performed during an 18 month period spanning 1972 and 1973 Each patient underwent cardiac catheterization prior to surgery All patients were fasted for 12 hours and had not taken propranolol for at least 2 days and digoxin for 5 days prior to the study The subjects were premedicated 45 minutes before catheterization with 50 mg of meperidine 25 mg of promethazine and 0 4 mg of atropine All pressure measurements were recorded on an Electronics for Medicine DR 12 from a P 23 DB Statham strain gauge connected to a fluid filled polyethylene catheter Left ventricular end diastolic pressure (LVEDP) was recorded at high amplification and at a paper speed of 100 mm per second LVEDP was measured at the point of rapid rise in pressure after the a wave or at the peak of the R wave on the electrocardiogram (ECG) Aortic pressure was electronically meaned Cardiac output was determined by the green dye or thermodilution indicator technique * Stroke work index was calculated from the formula SWI = (aortic mean pressure − LVEDP) × stroke volume index × 1 36/100 All measurements were obtained prior to the use of any contrast agent The ventriculogram was performed by injecting 0 8 ml per kilogram or 60 ml (whichever was less) of methylglucamine diatriazoate (Renografin 76) through a polyethylene pigtail catheter over a 4 second period The patients were positioned in the right anterior oblique and ejection fractions were calculated from this single plane by the area length method The hemodynamic measurements were repeated 3 to 5 minutes following left ventricular angiography The volume stress from the hyperosmotic contrast material used produces changes in LVEDP and stroke work index so that ventricular function curves can be constructed * Coronary arteriograms were done after ventriculography by Judkin s technique Narrowing of a major coronary artery of greater than 50 per cent of the diameter was considered significant The patients were restudied an average of 5 months (range 3 to 9 months) following their coronary artery surgery The restudy protocol was identical to the preoperative study and also included angiographic demonstration of graft patency Treadmill stress tests were performed when possible before each study The exercise protocol has previously been reported * There were 76 patients

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Table I Pre and postoperative ventricular function data (± S E M)

	Group	LVEDP preangio (mm Hg preop postop)	LVEDP postangio (mm Hg preop postop)	CO preangio (L min preop postop)	CO postangio (L /min preop postop)	Aortic mean preangio (mm H, preop postop
A	All patients	10±1–9±1	20±1–19±1	6 1±0 3–6 1±0 4	7 6±0 3–6 9±0 4	96±?–91+3
B	Stable angina	10±11–9+1	19±1–19±2	5 7±0 3–5 9±0 5	7 0±0 3–6 6±0 4	99±5–94 4
C	Unstable angina	8±1–9±2	20±6–22±2	8 5±1 0–6 8±1 4	9 8±0 6–8 0±1 5	9 ± –94±4
D	Previous infarct	10±1–11±1	22±2–22±2	6 5±0 6–5 6±0 4	7 5±0 5–6 2±0 4†	99±6–95 5
E	No previous infarct	9±1–7±1†	18±2–16±1	5 8±0 3–6 6±0 6	7 7±0 4–7 6±0 6	93±4–89±3
F	Poor preop function	14±1–12±2	25±2–24±2	5 6±0 7–5 0±0 4	6 5±0 7–5 9±0 5	89±5–5 4‡
G	Fair preop function	10±1–8±1	21±2–18±2	6 1±0 4–6 3±0 8	7 6±0 3–6 5±0 4	99±5–97–6
H	Good preop function	8±1–9±1	16±2–17±1	6 5±0 6–6 6±0 6	8 2±0 6–7 9±0 7	96±6–93 4
I	Operated for markedly positive stress test	10±1–9±2	22±2–17±2	5 6±0 3–6 2±0 7	7 5±0 8–7 0±0 8	86±4–84 9
J	Stress test >2 mm	10±1–9±1	23±2–16±2†	5 4±0 2–5 8±0 5	7 5±0 5–6 8±0.5	95±5–97–
K.	Main left lesion	11±1–9±1	24±3–19±1	5 3±0 4–6 7±1 3	7 3±0 9–6 5±0 3	99±8–95 8
L	No periop infarct	9±1–9±1	19±2–18±1	5 9±0 5–6 2±0 4	7 6±0 5–7 2±0 5	93±5–95+4
M	Periop infarct	11±1–9±1	22±2–20±2	6 5±0 4–6 1±0 8	7 6±0 5–6 5±0 5*	99±5–85–5‡
N	One or more grafts closed	11±1–8±1*	22±2–19±2	6 1±0 3–5 9±0 6	7 4±0 3–6 6±0 4‡	95±5–81–5‡
O	100% graft patency	9±1–10±1	18±2–18±1	6 1±0 6–6 4±0 5	7 8±0 6–7 2±0 7	97±5–101 3
P	No periop infarct and 100% patency	9±1–9±1	19±2–18±1	5 9±0 6–6 5±0 5	7 7±0 6–7 4±0 7	95±5–99±4
Q	Asymptomatic postop	9±1–9±1	19±1–19±1	6 3±0 4–6 2±0 5	7 7±0 4–7 1±0 4	93±4–91+3
R	Neg stress test postop	9±1–9±1	21±2–18±1	6 3±0 5–6 4±0 6	7 8±0 5–6 9±0 3	96±–94±5
S	Ischemic postop	11±1–8±1‡	21±3–18±2	6 1±0 5–6 1±0 8	7 6±0 6–7 4±0 9	100±6–88
T	Change in native circulation	10±1–9±1	19±1–19±1	6 3±0 4–6 2±0 6	7 7±0 4–6 9±0 5	97±5–88 4
U	No change in native circulation	10±1–9±1	23±4–20±2	5 9±0 5–6 0±0 5	7 4±0 7–7 0±0 7	90±4–91–4

p < 0 05 § p < 0 001
† p < 0 02 ¶ p < 0 0001
‡ p < 0 01 || p < 0 00001

who underwent coronary bypass grafting during the protocol period There were 6 operative deaths Thirty nine patients were excluded from the study because preoperative or postoperative catheterization data were incomplete and one patient was lost to follow up

Results

The 30 patients in this study were all male Eighteen (60 per cent) were operated on because of severe but stable angina uncontrolled by medical management Five (17 per cent) had unstable angina that did not stabilize after admission to the coronary care unit Seven patients (23 per cent) had a markedly ischemic response to exercise (greater than 2 mm ST segment depression) and were operated on because they had angina and a main left coronary obstruction, a main left equivalent (proximal obstruction of left anterior descending and circumflex coronary arteries), or severe three vessel disease Preoperative coronary arteriography demonstrated three vessel disease in 20 patients (67 per cent) two vessel disease in seven (23 per cent), and one vessel disease in three (10 per cent) In one case only the right coronary was bypassed but it supplied an unusually large portion of the posterolateral wall of the left ventricle One patient received four grafts (3 per cent), 15 three grafts (50 per cent) 10 two grafts (33 per cent) and four only one graft (14 per cent) Revascularization was considered to be complete in 25 (83 per cent) of the patients

At the time of restudy 24 patients (80 per cent) denied symptoms and six (20 per cent) had residual angina but stated it was improved

Postoperative treadmill stress tests were negative for ischemia in 15 and positive in five Stress tests either were not obtained in the other 10 patients or were technically inadequate for interpretation Perioperative infarcts defined as new Q waves on postoperative FCG s were noted in 12

I continued

rtic mean s.angio rs nm. Hg (± preop ± postop)	HR preangio (b/min preop postop)	HR postangio (b/min preop postop)	SV preangio (mL preop postop)	SV postangio (ml preop postop)	SWI preangio (Gm M/M preop postop)	SWI postangio (Gm M/M preop postop)	Ejection fraction (% preop postop)	No
4-97±3	8±?-89±3‡	8?±3-87±3	80±4-70±5	9?±4-81±5‡	50±3-41±3†	57±3-44±3‡	6?±3-62±2	30
5-93±4	80±3-91±3†	8?±5-88±3	75±5-66±6	88±5-76±6	48±4-39±3	54±3-43±3‡	64±3-63±3	18
10-103±8	78±1-8?±3	79±5-84±4	100±9-82±18	114±7-7?±6	66±11-49±11	74±11-51±8	64±6-5?±7	5
7-100 6	81±4-84±3	84±4-85±3	78±6-68±7	87±5-73±7	5?±6-41±4	?8±5-40±4‡	58±4-?8±3	14
?-94-4	75± -94±5‡	80±4-89±4	8?±4-71±7	10?±6-86±?†	48±2-40±4	57±4-47±3‡	66±3-66±3	16
?-8? 3	8±?-80±5	76±5-83±4	72±4-61±8	84±3-69±10	40±3-31±3‡	44±3-33±4	43±?-61±8‡	6
6-101-6	77±3-93±4‡	87±5-89±3	8?±3-69±9	93±4-75±6†	55±5-4?±6	5?±5-43±4	66±11-?9±4	12
? 100±4	8±5-90±6	79±5-89±5	83±9-75±6	104±10-93±9	?0±6-44±3	66±5-50±4‡	68±2-66±2	12
?-89+8	72±3-89±10	75±4-89±8	78±5-70±3	101±11-76±4†	43±4-38±5	54±7-41±6	57±6-6?±5	7
?-9 ±6	73±7-91±6†	80±3-89±5	74±4-64±3‡	96±7-76±3‡	44±3-38±4	55±6-43±4†	60±4-6?±4	11
9-104-7	72±2-8?±4‡	76±5-83±4	73±5-77±12	99±13-79±4	46±5-46±6	56±10-49±4	63±4-69±5	6
6-98-4	78±3-90±5	84±5-94±7	7?±6-70±4	94±7-8?±7	47±4-4?±3	59±5-46±3†	64±3-6?±3	18
?6-94-6	77±3-88±3	8±3-87±3	84±4-69±10	97±4-75±8‡	53±4-39±6†	57±5-40±4‡	59±5-57±4	12
?6-9?+4	8±3-86±3	80±4-85±3	79±4-69±7	93±5-79±7‡	47±3-37±5†	52±3-41±3‡	59±4-60±4	16
?5-101±4	77±4-93±5†	84±5-90±4	81±6-71±6	106±9-83±8‡	53±6-44±3	64±6-47±4†	65±2-64±3	14
?5-101±4	?±3-94±6‡	84±6-90±5	9±7-72±6	99±9-85±8	50±6-44±3	60±6-49±4	64±2-64±3	12
5-9?-4	79±3-89±4	83±4-89±3	80±4-71±5	96±5-82±6‡	49±4-40±3	?6±4-43±3‡	64±3-61±3	24
?6-97±	73±3-9?-5‡	79±3-89±4	84±5-71±6	99±6-79±3‡	53±5-41±4†	59±5-42±3‡	64±3-62±3	15
? -96±	1±?-84±5	7?±3-81±3	85±6-73±11	10?±8-91±13	53±5-43±7	61±4-50±5	58±6-68±4	9
5-9 +4	?±3-94±4‡	81±4-9?±3†	85±4-68±6‡	98±4-77±5¶	51±4-36±3‡	60±4-39±3‡	61±3-60±3	19
?6-100±4	78±3-80±3	80±4-78±3	76±6-75±9	94±10-89±11	49±6-50±5	5?±6-5?±5	64±6-66±4	10

patients (40 per cent) Postoperative coronary arteriography demonstrated patency in 53 of the 3 grafts placed (73 per cent)

The purpose of this study was to investigate any changes in ventricular function following coronary artery bypass surgery and elucidate their causes Global ventricular function was evaluated by developing pre and postoperative ventricular function curves from the volume stress of left ventricular angiography and by measuring pre and postoperative ejection fractions Previous work has shown that hyperosmotic contrast material produces increases in cardiac output presumably due to increases in blood volume The increased blood volume results in greater venous return and increased ventricular end diastolic volume Cardiac output is thereby enhanced by the Frank Starling mechanism The resultant changes in cardiac output and LVEDP make the construction of ventricular function curves possible[4] Table I includes the determinants of the ventricular function curves (LVEDP and SWI) ejection fractions (EF) and the hemodynamic values that influence these measurements cardiac output (CO) mean aortic pressure heart rate (HR) and stroke volume (SV) Pre and postoperative values are listed side by side with the standard error of the mean (S E M) Any statistically significant differences are annotated Line A of Table I indicates the mean values for the entire group There were significant decreases in pre and postangiogram SWI postoperatively Since there was no change from pre to postoperative LVEDP depression of the ventricular function curve occurred after surgery (Fig 1) There was no change in postoperative EF A significant increase in postoperative resting HR was observed

In an attempt to obtain a more meaningful understanding of changes in postoperative ventricular function patients were grouped according to indications for operation condition prior to oper

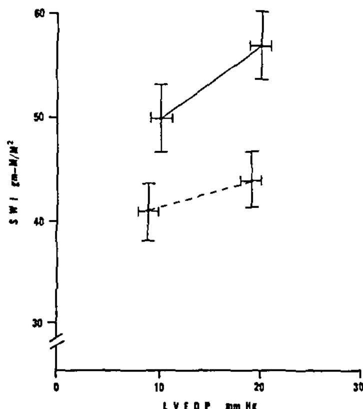


Fig 1 Pre and postoperative ventricular function curves for all patients Solid line = preoperative broken line = postoperative *SWI* = stroke work index *LVEDP* = left ventricular end diastolic pressure

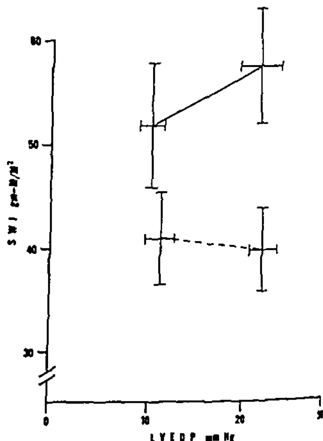


Fig 2A Pre and postoperative ventricular function curves in patients with prior myocardial infarction Solid line = preoperative broken line = postoperative *SWI* = stroke work index *LVEDP* = left ventricular end-diastolic pressure

ation, intraoperative events, and postoperative status These categories are included in Table I

Separating patients by type of preoperative angina (stable, Group B, unstable, Group C) did not alter the effect of bypass surgery on postoperative ventricular function There was evidence for depression of function in both groups although the number of patients with unstable angina was too small for statistical significance

A history of an old myocardial infarction prior to surgery (Group D) was associated with a greater depression of the postoperative ventricular function curve, but a significant decrease in function occurred in the patients without previous infarction (Group E, Figs 2*A* and 2*B*) Ejection fractions were unchanged after surgery but were lower in the infarct group The group without previous infarction had a significant increase in postoperative heart rates whereas the infarct group did not

Patients were categorized as having poor, fair, or good preoperative ventricular function (Groups F, G, and H) Patients with resting LVEDP s of 12 mm Hg or less, ejection fractions

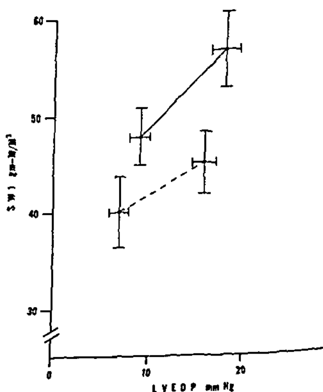


Fig 2B Pre and postoperative ventricular function curves in patients without prior myocardial infarction Symbols as in Fig 2*A*

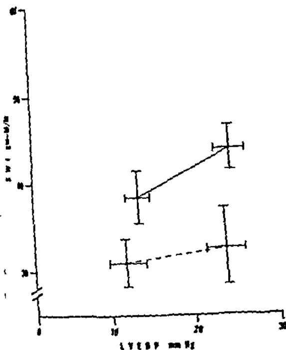


Fig 3A. Pre- and postoperative ventricular function curves in patients with poor preoperative ventricular function Solid line = preoperative broken line = postoperative SWI = stroke work index LVEDP = left ventricular end diastolic pressure

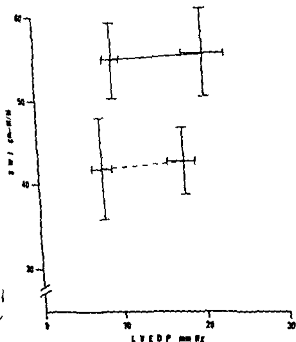


Fig 3B Pre and postoperative ventricular function curves in patients with fair preoperative ventricular function Symbols as in Fig 3A

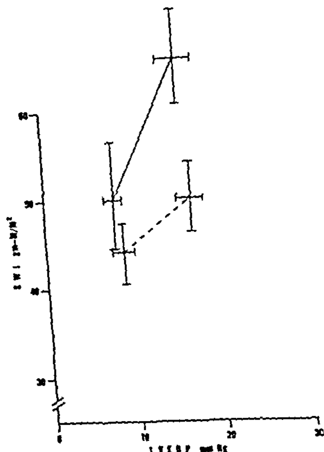


Fig 3C Pre- and postoperative ventricular function curves in patients with good preoperative ventricular function Symbols as in Fig 3A

55 per cent or greater, and normal preoperative ventricular function curves were rated as good patients meeting none of these criteria as poor and the remainder as fair Postoperative ventricular function curves were depressed by equivalent amounts in all groups (Figs 3A 3B and 3C) Postoperative ejection fractions were significantly increased (43 to 61 $p < 0.01$) in patients with poor preoperative ventricular function however there was a significant decrease in postoperative aortic mean pressure in this group Ejection fraction did not change significantly in patients with fair or good preoperative ventricular function

There was a group of patients with evidence of a rather markedly ischemic ventricle preoperatively as defined by very positive stress tests (greater than 2 mm ST segment depression) Many of these patients (five of 11) had significant main left coronary obstruction Seven of these

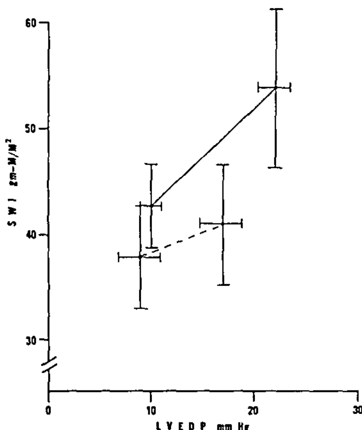


Fig 4A Pre and postoperative ventricular function curves in patients with evidence of markedly ischemic ventricular function preoperatively (markedly positive stress test) Solid line = preoperative broken line = postoperative *SWI* = stroke work index *LVEDP* = left ventricular end diastolic pressure

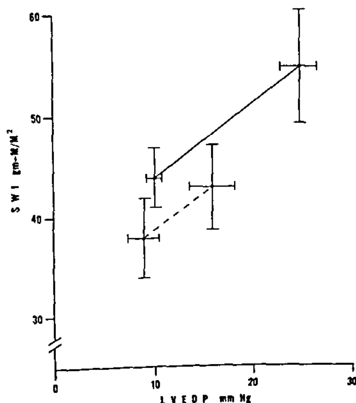


Fig 4B Pre and postoperative ventricular function curves in patients with evidence of markedly ischemic ventricular function preoperatively (stress test > 2 mm) Symbols as in Fig *4A*

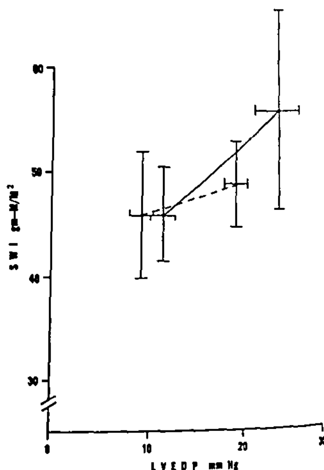


Fig 4C Pre and postoperative ventricular function curves in patients with evidence of markedly ischemic ventricular function preoperatively (main left lesions) Symbols as in Fig *4A*

patients were operated on primarily because of the markedly positive stress test Their angina was mild or moderate and not sufficient to be considered as indication for operation alone (Group I) They had severe three vessel disease main left lesions or main left equivalent lesions While there was a decrease in stroke work index postoperatively there was also a significant decrease in postoperative LVEDP after angiography For this reason, the postoperative ventricular function curve was only slightly depressed (Fig *4A*) There was a significant improvement in the ejection fraction from 57 to 65 ($p < 0.05$) and the postoperative aortic mean pressure was unchanged All patients with preoperative stress tests showing greater than 2 mm ST segment depression (Group J) had a decrease in postoperative stroke work index but this also was associated with a significant decrease in postangio LVEDP so the ventricular function curve was changed little after surgery (Fig *4B*) The ejection fraction increased from 60 to 65 but this was not statistically significant Patients with signifi

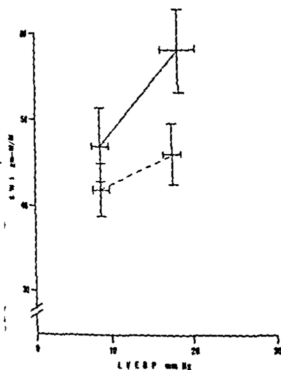


Fig 5A. Pre and postoperative ventricular curves in patients without a perioperative infarct Solid line = preoperative broken line = postoperative *SWI* = stroke work index *LVEDP* = left ventricular end-diastolic pressure

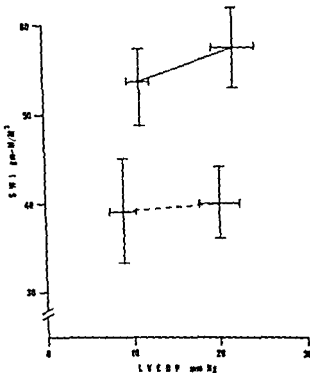


Fig 5B Pre and postoperative ventricular curves in patients with perioperative infarct Symbols as in Fig 5A

cant main left coronary lesions (Group K) had no postoperative depression of the ventricular function curve (Fig 4C) and ejection fraction improved but not to levels of statistical significance

A perioperative infarct could be expected to depress postoperative ventricular function However patients without a perioperative infarct (Group L) likewise had significant depression of postoperative ventricular function The perioperative infarction groups, however did have a greater reduction in postoperative stroke work indices (Group M Figs 5A and 5B) Ejection fractions were unchanged in both groups

The finding of one or more closed grafts at restudy (16 patients) was associated with a depressed postoperative ventricular function curve (Group N Fig 6A) Only four patients had all grafts occluded The 14 patients with 100 per cent graft patency (Group O) also had significantly lower postoperative ventricular function curves (Fig 6B) Even patients who did not have a perioperative infarct and had 100 per cent patency on restudy (Group P) were found to have depressed ventricular function curves postoperatively (Fig 6C) Ejection fractions were unchanged after surgery in these three groups.

Lack of myocardial ischemia postoperatively whether the subjective lack of anginal symptoms (24 patients Group Q) or more objectively a negative treadmill stress test (15 patients Group R) did not prevent depression of ventricular function curves However the presence of angina and/or a positive stress test (nine patients Group S) after surgery appeared to produce contradictory data There was a decrease in the postoperative stroke work indices but ejection fraction and LVEDP improved. However there was a significant decrease in postoperative aortic mean pressure in these patients Similar results were previously noted in the patients with poor preoperative ventricular function (Group F) When all patients were categorized according to changes in postoperative ejection fraction the group of patients with improved ejection fractions showed a significant decrease ($p < 0.01$) in postoperative aortic mean pressure (Table II)

Finally in this study the most important determinant of postoperative ventricular function was the state of the native circulation at

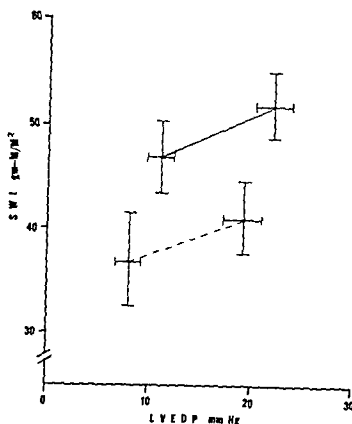


Fig 6A Pre and postoperative ventricular function curves in patients with graft closure (one or more grafts occluded) Solid line = preoperative broken line = postoperative *SWI* = stroke work index *LVEDP* = left ventricular end diastolic pressure

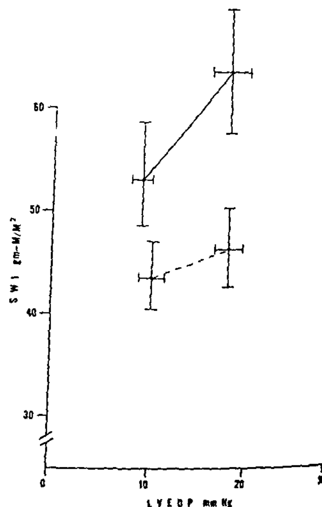


Fig 6B Pre and postoperative ventricular function curves in patients with 100 per cent graft patency Symbols as in Fig 6A

Table II Effect of aortic pressure on ejection fraction

	Postop EF increased 5% or more (n = 10)		*Postop EF unchanged (n = 10)*		*Postop EF decreased 5% or more (n = 9)*	
	Preop	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
Aortic mean	94	83	99	98	93	93
S E M	6 4	6 6	6 5	[illegible] 3	4 6	3 9
p value	< 0 01		< 0 5			< 0.5

recatheterization The 19 patients (Group T) who demonstrated progression of preoperative obstructions (10 per cent increase or more), or a new occlusion in the native circulation showed the most significant depression in postoperative ventricular function (Fig 7*A*) The changes were 100 per cent occlusion of a previously patent vessel in 24 instances and an increase in a preoperative obstruction in six instances In 18 patients at least one of the changes was a new complete occlusion Twenty two (73 per cent) of these changes were associated with a patent graft distal to the change seven (23 per cent) with an occluded graft and one (4 per cent) change in native circulation occurred in an ungrafted area The 10 patients without a change in postoperative native circulation (Group U) had no evidence by any parameter of deterioration in ventricular function (Fig 7*B*) The group with the progression of disease in native circulation demonstrated very significant increases in heart rate and decreases in aortic mean pressures post

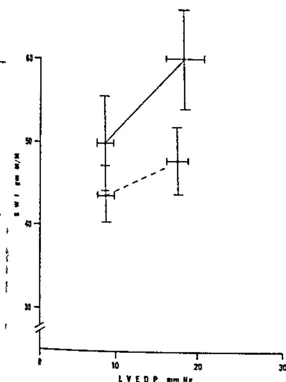


Fig 6C Pre and postoperative ventricular function curves in patients with 100 per cent graft patency plus no perioperative infarct Symbols as in Fig 6A

operatively One patient did not have the native circulation opacified adequately enough at restudy for interpretation

Discussion

There continues to be controversy as to the effects of coronary artery bypass surgery on left ventricular function Some studies have demonstrated improvement others no change and still others have shown deterioration The data from our entire group would suggest there has been some deterioration of ventricular function following coronary bypass surgery It is evident that the patients having this operation are not a homogeneous group and this may in part explain the conflicting reports in the literature on the effects of this operation on ventricular function Therefore we subdivided our patients into groups according to the indications for operation condition prior to operation intraoperative events and postoperative status Symptomatology and the quality of ventricular function preoperatively were of some prognostic value in predicting the effect of the operation on postoperative function Patients with a history of a previous infarct had poorer postoperative ventricular function than patients who did not However patients without prior infarctions also demonstrated decreased postoperative function as a group (Figs 2A and 2B) The group of patients with the best chance of maintaining ventricular function were those with very ischemic ventricles preoperatively as evidenced by markedly positive stress tests This group included patients with significant main left coronary artery lesions They showed improvement in postoperative ejection fractions without decreases in aortic mean pressure They did have lower values for pre and postangiogram stroke work index at restudy but left ventricular end diastolic pressures were also lower so there was little or no change in the ventricular function curve (Figs 4A 4B and 4C) Therefore in this group of patients there was no significant deterioration in ventricular function and by some criteria an improvement was noted

The patients who sustained a perioperative infarction or were shown to have one or more grafts occluded postoperatively could be expected to show a decrease in postoperative ventricular function However patients who did not have a perioperative infarct who had 100 per cent graft patency or both also demonstrated a significant depression in postoperative ventricular function curves (Figs 5A 5B 6A 6B and 6C)

The most important predictor of the state of postoperative ventricular function was the condition of the native coronary circulation at restudy The majority of the changes in the native circulation were progression to 100 per cent occlusion of a coronary artery proximal to a patent graft a common finding reported by others[10-1] This group showed a very significant depression in postoperative ventricular function curves (Fig 7A) If there was no change in native circulation postoperative hemodynamic values were virtually identical to those of the preoperative study (Fig 7B) The observation that partially obstructed coronary arteries occlude proximal to a patent vein graft has not caused much alarm [2] However the data presented here would suggest that these occlusions have a very detrimental effect on ventricular function Possibly small branches near the obstruction are lost with the occlusion and viable myocardium is sacrificed resulting in loss of ventricular function In any

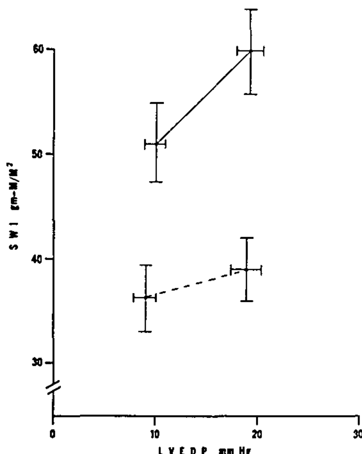


Fig 7A Pre and postoperative ventricular function curves in patients with postoperative changes in native coronary circulation Solid line = preoperative broken line = postoperative SWI = stroke work index $LVEDP$ = left ventricular end diastolic pressure

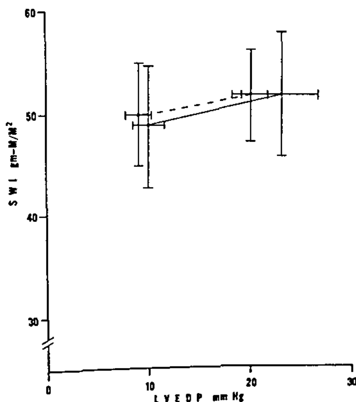


Fig 7B Pre and postoperative ventricular function curves in patients without postoperative changes in native coronary circulation Symbols as in Fig 7A

regard the maintenance of a patent native circulation is somehow important to the preservation of myocardium in the grafted area even in the presence of a patent graft

The incidence of perioperative infarction was 2½ times greater in the patients with changes in native circulation (53 per cent) than in patients without changes in native circulation (20 per cent) This would suggest that the loss of myocardium due to infarction may occur when the native circulation occludes even though a patent graft may be present distal to the occlusion Comparison of groups with and without ECG evidence of myocardial infarction (L and M) was not as discriminating as changes in native circulation This may be related to the insensitivity of ECG to recognize new myocardial damage in the postoperative period Vectorcardiographic[14] and enzyme[15] techniques suggest that the incidence of perioperative infarction may be quite high in this operation The incidence of perioperative infarction by ECG was unusually high (40 per cent) in the group of patients restudied This may well bias the entire group toward worse postoperative ventricular function However, the purpose of this study was to determine factors that influence ventricular function following bypass surgery Perioperative infarction by ECG criteria is only one factor that affects postoperative function and comparison of Groups L and M indicates that it is not the most differentiating

The patients who had either angina a positive stress test, or both postoperatively (Group S) had an increased ejection fraction and a reduction in LVEDP postoperatively This could be interpreted as an improvement in ventricular function in a group of patients in whom deterioration might well be expected However this group also had a significant drop in resting aortic mean pressure and decreased afterload is known to improve ejection fraction and LVEDP[11] Stroke work indices however were depressed postoperatively in these patients

These observations prompted us to further investigate the relationship of postoperative changes in resting aortic mean pressure on changes in ejection fraction It was found that the patients with improved postoperative ejection fractions as a group had a significant decrease in baseline aortic mean pressure (Table II) The cause of the lower postoperative aortic mean pressures in our patients is unknown It is possible

that this represents a compensatory mechanism to preserve cardiac output in a group of patients who have further depression of ventricular function after bypass surgery Another unexplained observation in our patients is the increased resting heart rate postoperatively This has been reported by others[1, 4] The explanation that it is due to a high catecholamine state from the stress of operation does not seem plausible in a group of patients studied an average of 5 months after surgery and this increase in heart rate has been observed by others as late as 1 year postoperatively This could represent a baroreceptor reflex because of lower aortic pressure The observation that a drop in postoperative aortic mean pressure correlates with improved ejection fraction makes it imperative that this hemodynamic parameter be known before interpreting increased ejection fractions after surgery as improved ventricular function

Since our patients often had increases in postoperative heart rate with concomitant decreases in stroke volume and often with decreases in blood pressure it is apparent that the decreases in stroke work index would occur However these changes should have produced an appropriate decrease in LVEDP according to the Frank Starling mechanism unless there had been alterations in ventricular function or compliance The fact that LVEDP did not decrease postoperatively explains the postoperative depression of ventricular function curves seen in many of our patients

Conclusion

Many of the patients in this study demonstrated depressed ventricular function after coronary artery bypass surgery The most important determinant of deterioration was a new occlusion in the native circulation even though the majority of patients had a patent graft distal to the new occlusion Patients with very ischemic ventricles preoperatively appear to have the best chance of showing maintenance or improvement in postoperative ventricular function Caution must be used in interpreting increases in postoperative ejection fraction as improvement in ventricular function because of the often seen decrease in postoperative aortic mean pressure This decrease in aortic pressure may explain the increased postoperative heart rate observed by us and others

Summary

Ventricular function was evaluated by the development of ventricular function curves from the volume stress of angiographic contrast media in 30 patients before and an average of 5 months after coronary bypass surgery Patients were grouped according to preoperative operative indications perioperative events and postoperative status to determine the most important factors affecting postoperative ventricular function Progression of lesions in the native coronary circulation correlated most significantly with a decrease in postoperative ventricular function In 18 of 19 patients the changes in native coronary circulation were progression to complete occlusion Seventy three per cent of these changes were associated with a patent graft distal to the change Patients with very ischemic ventricles as evidenced by a markedly positive stress test (> 2 mm ST depression) and/or main left coronary obstruction maintained or improved postoperatively ventricular function Increase in postoperative ejection fraction was often associated with decrease in aortic mean pressure making it difficult to use this parameter to evaluate postoperative ventricular function

REFERENCES

1 Itscoitz S B Shepherd R L, Glancy D L, Oldinger G N Stinson E B and Epstein S E Deterioration of myocardial function following aortocoronary bypass operation (abst) Clin Res 21 4?7 1973
2 Campeau L Ghanem E, E plugas, E Lesperance J Bourassa M and Grondin C M Left ventricular performance during exercise before and one year after aortocoronary bypass for angina pectoris, Circulation 49 50 (Suppl II) 103 1974
3 Rees G Bristow J D Kremkau E L Green G S Herr R H Griswold H E, and Starr A Influence of aortocoronary bypass surgery on left ventricular performance N Engl J Med 284 1116 1971
4 Hammermeister K E Kennedy J W, Hamilton G W, Steward D K Gould K L Lipscomb K and Murray J A Aortocoronary saphenous vein bypass Failure of successful grafting to improve left ventricular function in chronic angina N Engl J Med 290 183 1974
5 Chatterjee K, Swan H J C Parmley W W Sustaita H Marcus H S and Matloff J Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease With and without previous myocardial infarction Circulation 47 276 1973
6 Symposium on indocyanine green and its clinical applications Proc Staff Meet Mayo Clin 35 729 1960
7 Ganz W Donoso R Marcus, H S Forrester J S and Swan H J C A new technique for the measurement of cardiac output by thermodilution in man Am J Cardiol 27 39 1971
8 Brundage B H and Cheitlin M D Ventricular func

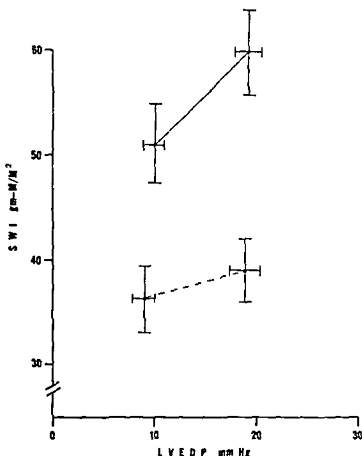


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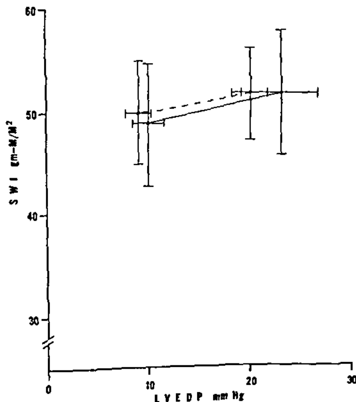


Fig 7B Pre and postoperative ventricular function curves in patients without postoperative changes in native coronary circulation Symbols as in Fig 7A

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Electrocardiographic and vectorcardiographic abnormalities in Fabry s disease

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Fabry s disease is an X linked disorder of glyco sphingolipid metabolism related to the defective activity of alpha galactosidase A[1] There is deposition of glycosphingolipid mainly trihexosyl ceramide in the vascular smooth muscle myocardium cells of sympathetic central nervous system and epithelial cells of renal glomeruli[1] Because of unusual skin lesions and multiorgan involvement the disease is also known as angio keratoma corporis diffusum universale Involvement of the myocardium and small blood vessels has long been recognized[2] Electrocardiographic (ECG) abnormalities have occasionally been reported[6,10,11] but there is no detailed information regarding the incidence of ECG and vector cardiographic (VCG) abnormalities in these patients The purpose of this report is to review the ECG in 32 patients and the VCG in 15 patients with Fabry s disease followed in our institution

Materials and methods

Thirty two patients between the ages of 6 and 56 years with Fabry s disease (including 21 hemizygotes and 11 heterozygotes) studied at the University of Minnesota Hospitals form the basis of this report The diagnosis of hemizygosity and heterozygosity for Fabry s disease was made by physical examination corneal changes as seen by slit lamp examination skin biopsy and biochemical studies which included measurement of trihexosyl ceramide concentration in plasma urinary sediment and the determination of alpha galactosidase activity in plasma leukocytes and tears[12,13] In each patient a 12 lead ECG and in 15 a corrected orthogonal VCG was performed[14] More than one ECG was performed in 13 patients over periods ranging from 3 to 12 years In two of the 13 patients with serial ECG s cardiac signs and symptoms were present both of these patients died and necropsy revealed extensive cardiac infiltration with glycosphingolipid characteristic of Fabry s disease[15] None of the other patients presented clinical signs or symptoms of cardiac disease and ECG/VCG abnormality if present was found only upon routine examination

ECG s were interpreted for rhythm QRS axis PR QRS and QT intervals and P QRS and ST T morphology according to the New York Heart Association criteria[16] and compared with ECG s of age matched normal subjects[17]

VCG s were recorded on magnetic tape and were analyzed with a minicomputer as previously reported[18] and interpreted according to established criteria[19]

Results

Of 32 patients there were 11 heterozygous females and 21 hemizygous males The mean age was 33 (range 19 to 56) and 22 (range 6 to 50) years respectively Table I shows the genotype and ECG abnormalities noted in these patients

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June 1977 Vol. 93 No 6 pp 699-705

tion curves from the cardiac response to angiographic contrast A sensitive detector of ventricular dysfunction in coronary artery disease AM HEART J 88 281 1974

9 Cheitlin M D Davia J E deCastro C M Barrow E A and Anderson W T Correlation of critical left coronary artery lesions with positive submaximal exercise tests in patients with chest pain AM HEART J 89 305 1975

10 Griffith L S C Achuff S C Conti C R Humphries J O Brawley R K Goth V L and Ross R S Changes in intrinsic coronary circulation and segmental ventricular motion after saphenous vein coronary bypass graft surgery N Engl J Med **288** 589 1973

11 Bousvaros G Piracha A R Chaudhry M A Grant C Older T M and Pifarré R Increase in severity of proximal coronary disease after successful distal aorto coronary grafts Its nature and effects Circulation 48 915 1973

12 Levine J A Bechtel D J Gorlin R Cohn P F Herman H V Cohn L V and Collins, J J Jr Coronary artery anatomy before and after direct revascularization surgery clinical and cinearteriographic studies in 67 selected patients AM HEART J 89 561 1975

13 Urschel C W Covell J W Sonnenblick E H Ross, J Jr and Braunwald E The effects of decreased aortic compliance on performance of the left ventricle Am J Physiol **214** 298 1968

14 Anderson W T Brundage B H and Cheitlin M D Vectorcardiographic changes following coronary artery bypass surgery AM HEART J 87 471 1974

15 Dixon S H Limbird B S Roe C R Wagner G S Oldham M D Jr and Sabiston D C Jr Recognition of postoperative acute myocardial infarction Application of isoenzyme techniques Circulation 47 48 (Suppl III) 137 1973

APC	VPC	MI	Follow up
+	–	–	–
–	–	–	–
–	–	–	–
–	–	–	Disappearance of RBB
–	–	–	None
–	–	–	None
–	–	–	–
–	–	–	–
–	–	–	–
–	–	–	–
–	–	–	–
–	+	–	Var PR interval SA block AF
–	–	–	–
–	–	–	–
+	–	–	–
–	–	–	–
–	–	–	PR interval 120 msec
–	–	–	PR interval 140 msec RBBB QRS axis –45
+	+	–	Variable PR inter AF
+	+	–	RBB PR inter 360 msec intermittent AF Wenckebach phenomena CHB
–	–	+	–
–	–	–	–
–	–	–	–
–	–	–	–
–	–	–	–
–	–	–	PR interval 140 msec
–	–	–	PR interval 140 msec
–	–	–	–
–	–	–	Incomplete RBBB LVH
–	–	–	PR interval 150 msec QRS 90
+	+	–	Sinus bradycardia 45/min VPCs
–	–	–	–

years All five patients with atrial fibrillation were hemizygous males One heterozygous female patient (No 31) initially had sinus rhythm (heart rate 80 per minute) and later developed sinus bradycardia (rate of 45 per minute) and frequent premature ventricular beats One 50 year old male patient (No 20) developed cardiac failure and preterminally had varying degrees of atrioventricular (A V) conduction defects i e Wenckebach phenomenon A V junctional escape rhythm A V dissociation associated with ventricular tachycardia and complete heart block

QRS axis The QRS axis was normal in 30 of the 32 patients In one patient (No 30–heterozygous) the QRS axis was +105° initially and later became +90° The remaining patient (No 18–hemizygous) fulfilled the ECG criteria of left anterior hemiblock with a change in axis from –27° to –45° over a follow up period of 4 years In both these patients the PR interval was 140 msec and the latter patient also developed a right bundle block pattern

PR interval In 26 of 32 patients the PR interval corrected for age and heart rate was within normal limits on initial examination In four patients the PR interval was 120 msec or less in the remaining two it could not be calculated because of the presence of atrial fibrillation In 13 patients in whom serial ECG s were available the PR interval shortened in two from 160 to 140 msec over a 1 to 3 year period (patients Nos 18 and 27) in one (patient No 17) it shortened from 140 to 120 msec over a 3 year follow up period In three patients (Nos 20 26 30) followed for 2 to 5 years the PR interval prolonged and one of these three (No 20–hemizygous) finally developed complete heart block In two (patients Nos 12 and 19) the PR interval was variable and they later developed atrial fibrillation in five patients the PR interval remained unchanged On initial examination four patients had PR intervals of 130 msec (lower limit of normal 127 msec for age and heart rate)

Conduction defects Six patients showed ventricular conduction abnormalities Four of these (Nos 18 and 20–hemizygous and Nos 25 and 29–heterozygous) initially showed nonspecific intraventricular conduction defect manifested by QRS duration over 100 msec Both hemizygous patients later developed a pattern of complete right bundle branch block and one heterozygous patient (No 29) developed incomplete right bundle branch block In two other hemizygous patients (Nos 4 and 12) incomplete right bundle branch block was present on the first examination In one (No 4) there was no evidence of block 6 months later None of the patients had left bundle branch block Sinoatrial block evolved in one hemizygous patient (No 12)

Chamber enlargement ECG evidence of chamber enlargement was most commonly seen for the left ventricle Ten patients showed a pattern of left ventricular hypertrophy (LVH) five of these fulfilling all criteria including strain[1] In five

Table I ECG's in Fabry's disease*

								LVH				Conduct defect	
No	Pt	Age Sex	Rhythm	HR	QRS axis	PR inter (msec)	LAE	Only volt	All crit	RVH	Non sp ST T chgs	IVCD	RBBB
Hemizygotes													
1	G T	6M	RSR	95	N	140	−	−	−	−	−	−	−
2	L C	11M	RSR	75	N	115	−	−	−	−	−	−	−
3	C L	11M	RSR	100	N	140	−	−	−	−	−	−	−
4	L R	12M	RSR	80	N	120	−	+	−	+	−	−	+
5	K G	14M	RSR	90	N	130	−	−	−	−	−	−	−
6	L D	15M	RSR	75	N	120	−	−	−	−	−	−	−
7	B R	16M	RSR	75	N	140	−	−	−	−	−	−	−
8	A H	18M	RSR	90	N	160	−	−	−	−	−	−	−
9	S R	19M	RSR	70	N	160	−	−	−	−	−	−	−
10	S L	23M	RSR	90	N	150	−	−	−	−	−	−	−
11	S J	29M	AF	90	N	−	−	−	+	−	−	−	−
12	G A	31M	RSR	80	N	140	−	−	−	−	−	−	+
13	D P	33M	RSR	85	N	160	−	+	−	−	−	−	−
14	S W	33M	RSR	95	N	160	−	+	−	−	−	−	−
15	G R	36M	RSR	80	N	140	−	−	−	−	+	−	−
16	G G	38M	RSR	90	N	140	−	+	−	−	−	−	−
17	G D	40M	RSR	80	N	140	−	−	+	−	−	−	−
18	R A	42M	RSR	65	−27	160	+	−	+	−	−	+	−
19	C J	47M	RSR	80	N	140	+	−	+	−	−	−	−
20	B C	50M	RSR	70	N	230	+	−	−	−	+	+	−
21	B M	51M	AF	160	N	−	−	−	−	−	−	−	−
Heterozygotes													
22	K J	19F	RSR	60	N	130	−	−	−	−	−	−	−
23	L C	20F	RSR	85	N	180	−	−	−	−	−	−	−
24	C L	24F	RSR	75	N	120	−	−	−	−	−	−	−
25	M G	35F	RSR	85	N	130	−	−	−	−	−	+	−
26	N M	37F	RSR	85	N	130	−	−	−	−	−	−	−
27	B L	40F	RSR	72	N	160	−	−	−	−	−	−	−
28	A D	44F	RSR	90	N	150	−	−	−	−	+	−	−
29	K B	45F	RSR	82	N	150	−	−	−	−	−	+	−
30	A V	46F	RSR	78	105	140	−	−	−	−	−	−	−
31	S E	50F	RSR	80	N	160	−	−	+	−	−	−	−
32	S L	56F	RSR	75	N	160	−	+	−	−	−	−	−

APC atrial premature contraction AF atrial fibrillation CHB complete heart block IVCD intraventricular conduction defect LAE left atrial enlargement LVH left ventricular hypertrophy MI myocardial infarction RVH right ventricular hypertrophy RBBB right bundle branch block RSR regular sinus rhythm RAE right atrial enlargement VPC ventricular premature beat

Rhythm Thirty patients on initial examination showed regular sinus rhythm with a rate ranging from 60 to 100 per minute Six patients revealed evidence of atrial and/or ventricular premature beats Two of these had occasional and three had frequent atrial premature beats, whereas two had occasional and two had frequent multiform ventricular premature beats Three patients in this group had both atrial and ventricular beats Although continuous monitoring for ectopic activity was not done atrial and/or ventricular premature beats appeared to be more frequent than normal on repeated ECG examinations Two patients (Nos 11 and 21) presented with atrial fibrillation and three developed atrial fibrillation on follow up One patient (No 19) who had sinus rhythm and left atrial enlargement developed atrial fibrillation during the 3 year period of observation in another patient (No 20) atrial fibrillation was present only intermittently A 31 year old male patient (No 12) developed sinoatrial block followed by atrial fibrillation after 2

o 1 after 1 year and evolved in two patients (No 10 and 14) The ECG was normal in patient o 1 all along and revealed LVH with strain in patient No 10 VCG in two patients remained unchanged over period of 1 year

Discussion

Ferrans and associates[7] and Becker and associates have described the pathologic and ultrastructural features of the heart in Fabry's disease They found extensive glycosphingolipid deposits in the myocardial fibers connective tissue of each cardiac valve conduction system the endothelium and smooth muscle of large and small arteries They postulated that the glycosphingolipid infiltration was responsible for the cardiac abnormalities found in these patients Mitral and aortic valvular lesions have been described in Fabry's disease[3,9,11] and occasionally are responsible for the patient's death Nevertheless there have been limited descriptions of the ECG in these patients and include short PR interval left ventricular enlargement and nonspecific ST T changes[3] Atrial fibrillation complete heart block left anterior hemiblock and myocardial infarction patterns have also been occasionally reported[6,1] However morphological proof of infarction has rarely been provided

In our series six patients (19 per cent) had an abnormal rhythm either when first seen or during follow up examination Five were hemizygotic and one heterozygotic for Fabry's disease One showed sinus bradycardia Wenckebach phenomenon and complete heart block one heterozygous female developed sinus bradycardia Rhythm disturbances and sinoatrial block have been reported by several authors[2,6,1] Chamber enlargement and deposition of glycosphingolipid in the atria and around the conduction system is probably responsible for the rhythm disturbance Longer duration of the disease in our patients resulted in severe degree of A V block probably because of progression of the disease and more extensive deposition of glycosphingolipid in and around the conduction pathways Further proof of more severe degrees of cardiac abnormalities with longer duration of disease comes from the fact that older patients with Fabry's disease had more abnormalities on the ECG's and VCG's (Tables I and II) than their younger counterparts Ectopic beats arising in the atrium ventricle or both probably have their genesis in the same abnormality

A short PR interval has been described in Fabry's disease[3,8] Indeed in our series 13 per cent had a PR interval of 120 msec or less when first seen Follow up ECG's in 13 patients revealed that the PR interval shortened in three prolonged in three degenerated into atrial fibrillation in two and remained unchanged in five patients In a report by Roudebush and associates glycosphingolipid accumulation in the conduction system was proposed as a cause of short PR interval in Fabry's disease In the autopsy study by Becker and associates[1] deposits of glycosphingolipid were seen in cells of the sinus node the A V node His bundle and left and right bundle branches It is likely that lipid deposits in and around the A V pathway may alter conduction time However the presence of a short PR interval in five of 32 patients with Fabry's disease would require the presence of either abnormal short circuiting pathways or supernormal conduction through the normal pathways Prolongation of PR interval in three of 13 patients on follow up examination is most likely due to the progression of the disease process however progressive shortening in three others cannot be explained by this mechanism Probably the variations in PR interval result from glycosphingolipid deposition in nerves and nerve membranes causing instability in the conduction process[9]

Right and left axis deviation were present in one patient each Six patients (19 per cent) had evidence of intraventricular conduction defects most frequently right bundle branch block None of our patients had left bundle branch block Similar conduction abnormalities have been observed in other glycosphingolipid storage disorders including Sandhoff's disease[21] and G_{M1}[22] and G_{M2}[3] gangliosidoses It is likely that lipid deposits in and around the conduction system in Fabry's disease result in axis shift and conduction defects as in other storage disorders

As is apparent from Tables I and II the left ventricle is the most common chamber to be enlarged—38 per cent of all patients Criteria for left atrial enlargement were met in three patients on ECG and right atrial enlargement in one patient on VCG ST T segment changes were observed rather frequently in 10 of 32 patients In

Table II VCG findings in Fabry's disease

No	Pt	Age sex	PR int (msec)	QRS duration	QRS axis	RAE	IVCD	LVH	MI	Nonsp ST chgs	ECG interpretation
1	B R	16M	134	112	43	–	+	+	–	–	Within normal limits
2	A H	18M	152	86	58	–	–	–	–	–	Within normal limits
3	S L	23M	151	101	46	–	–	–	–	–	Within normal limits
4	S J	29M	–	102	23	–	–	–	–	+	Nonspecific ST T chan atrial fibrillation
5	S W	33M	166	100	33	–	–	+	–	–	LVH by voltage
6	D P	33M	166	100	27	–	–	–	–	–	LVH by voltage
7	G A	35M	139	96	70	–	–	–	–	–	Incomplete RBBB
8	G R	37M	134	76	29	+	–	–	–	+	Nonspecific ST T chan
9	G G	38M	146	89	24	–	–	+	*	–	LVH by volta e APCs
10	G D	40M	132	96	33	–	–	–	–	+	LVH
11	R A	44M	152	118	–5	–	+	+	–	–	Left axis IVCD LVH LAE
12	K J	19F	128	86	48	–	–	–	–	–	Within normal limits
13	N M	37F	118	93	32	–	–	–	–	–	Short PR interval
14	K B	49F	158	88	7	–	+	–	–	+	Incomplete RBBB LVH
15	S L	56F	135	109	15	–	–	+	–	–	LVH by voltage APCs

*Anterolateral wall

others voltage criteria alone for LVH were met Two patients (Nos 20 and 29) subsequently developed LVH after 1 and 3 years respectively Left atrial enlargement (LAE) was seen in three patients In one patient (No 4) right ventricular hypertrophy pattern was present associated with LVH Only two of 11 heterozygous females had chamber enlargement whereas nine of 21 hemizygous males had one or more enlarged chambers ($p < 0.05$)

Myocardial infarction Only one patient (No 21) showed a pattern of anteroseptal myocardial infarction, though there was no clinical evidence of myocardial damage This patient a 51 year old hemizygote had, in addition atrial fibrillation No other patient fulfilled ECG criteria of myocardial infarction

ST T changes These were present in five patients in association with left ventricular hypertrophy Three other patients had ST T changes, suggestive in two of myocardial ischemia in lateral chest leads In one patient (No 20) nonspecific ST T changes preceded development of left ventricular hypertrophy Two of these three patients were hemizygous and one heterozygous

Vectorcardiograms in Fabry s disease VCG s were available in 15 patients The genotypes of these patients and their VCG observations are shown in Table II In only five patients was the VCG normal One patient had atrial fibrillation (No 4) A PR interval of less than 120 msec was seen only in one patient (No 13) and six others had a PR interval between 120 and 140 msec Left ventricular hypertrophy and right atrial enlargement were seen in five patients and one patient respectively None had left atrial enlargement Four patients had evidence of nonspecific ST T changes and had no left ventricular hypertrophy One fulfilled criteria of anterolateral myocardial infarction on VCG but not on ECG An intraventricular conduction defect was present in three patients

Follow up VCG s Follow up VCG s were available on six patients In one patient (No 14) intraventricular conduction defect persisted and a pattern of LVH evolved after 2 months of observation The ECG in this patient continued to show incomplete right bundle branch block and left ventricular hypertrophy all along However 5 years earlier the ECG had revealed only intraventricular conduction defect In another patient (No 11) left atrial enlargement appeared and intraventricular conduction delay progressed to right bundle branch block and new left anterior hemiblock appeared Similar changes were also observed in his ECG as well Left ventricular hypertrophy disappeared in patient

abbreviated PR interval of Fabry's disease N Engl J Med. 289 357 1973.
Duncan, C. Angiokeratoma—a case with gross myocardial involvement, Australas Ann Med 19 58 1970
Leder A. A., and Bosworth, W C Angiokeratoma corporis diffusum universale (Fabry's disease) with mitral stenosis, Am. J Med 38 814 1965
Wise D Wallace H J and Jellinek E H Angiokeratoma corporis diffusum A clinical study of eight affected females Q J Med 31 177 1962
Ruiter M Pompen A. W. M and Wyers, H J G Über interne und pathologisch anatomische Befunde bei Angiokeratoma corporis diffusum (Fabry) Dermatologica 94 1 1947
Pompen A W M., Ruiter M and Wyers H J C Angiokeratoma corporis diffusum (universale) Fabry as a sign of an unknown internal disease Two autopsy reports, Acta Med. Scand 128 235 1947
Dubach, U C and Gloor F Fabry Kranheit (angiokeratoma corporis diffusum universale) Posphatidspeicher krankheit bei zwei Familien Dtsch Med Wohnschr 91 241 1966
Parkinson J E and Sunshine A Angiokeratoma corporis diffusum universale (Fabry) Presenting as suspected myocardial infarction and pulmonary infarcts, Am. J Med 31 951 1961
Becker A E Schoorl R Balk A G et al Cardiac manifestations of Fabry's disease Am J Cardiol 36 829 1975
Desnick, R. J Allen K Y Desnick S J et al Fabry's disease Enzymatic diagnosis of hemizygotes and heterozygotes. Alpha galactosidase activities in plasma serum leukocytes and urine J Lab Clin Med 81 157 1973
Johnson D L DelMonte M A Cottier E et al. Fabry's disease Diagnosis of hemizygotes and heterozygotes by alpha galactosidase A activity in tears Clin Chim. Acta 63 81 1975
Schmitt O H and Simonson, E The present status of vectorcardiography Arch. Intern Med 96 574 1955
15 Desnick, R J., Blieden L. C Sharp H L et al Cardiac valvular anomalies in Fabry's disease Clinical morphologic and biochemical studies Circulation (In press November 1976)
16 The Criteria Committee of the New York Heart Association Nomenclature and criteria for diagnosis of disease of the heart and great vessels ed 7 Boston 1973 Little Brown & Company
17 Altman P L., and Dittmer D S editors Respiration and circulation Bethesda Md 1971 Federation of American Societies for Experimental Biology p 281
18 Brohet C R., Liedtke C E., and Tuna N P wave abnormalities in the orthogonal electrocardiogram Correlation with ventricular overload in pulmonic and aortic valvular heart disease J Electrocardiol. 8 103 1975
19 Chou T C., and Helm R A. Clinical vectocardiography New York 1967 Grune & Stratton Inc
20 Ohnishi, A. and Dyck P J Loss of small peripheral sensory neurons in Fabry's disease Arch. Neurol. 31 120 1974
21 Blieden L. C., Desnick R J., Carter J B et al Cardiac involvement in Sandhoff's disease An inborn error of glycosphingolipid metabolism Am J Cardiol 34 83 1974
22. Hadley R N and Hagstrom J W C Cardiac lesions in a patient with familial neurovisceral lipidosis (generalized gangliosidosis) Am J Clin Pathol. 55 237 1971
23. Rodriguez Torres, R., Schneck L. et al. Electrocardiographic and biochemical abnormalities in Tay Sachs disease Bull. New York Acad. Med. 47 717 1971
24 Scholmerich, P Myocarditis and weitere Myokardiopathien in Bergman G Frey W., and Schwiegk H editors Handbuch er Inneren Medizin Berlin 1960 Springer Verlag p 960
25 Desnick R J Thorpe S R and Fiddler M B Towards enzyme therapy for lysosomal storage disease Phys. Rev 56 57 1976

seven ST T changes were associated with left ventricular hypertrophy and in three ST T changes were seen without left ventricular hyper trophy ST T changes were observed to precede left ventricular hypertrophy both by ECG and VCG in one patient ECG evidence of chamber enlargement can result from various mechanisms Left ventricular hypertrophy and ST T changes in many patients may result from hypertension secondary to renal involvement Infiltration of endothelium and myocardium by glycosphingo lipid [11, 15] may also result in ECG and VCG evidence of chamber enlargement in the absence of hypertension through some yet unidentified mechanisms Valvular involvement in Fabry s disease [5, 9, 11, 1] may also be responsible for chamber enlargement by volume or pressure overloading Nonspecific ST T changes may be a result of altered repolarization of the infiltrated myocardium

ECG evidence of myocardial infarction and ischemia have been occasionally reported in patients with Fabry s disease without clinical or autopsy evidence of coronary artery dis ease [6, 10, 11, 15] Our patients with either a pattern of myocardial infarction or ischemic T wave changes had no clinical features of coronary disease This again illustrates that storage disorders affecting the myocardium can mimick myocardial infarction in the ECG and VCG [1]

As would be expected hemizygosity was asso ciated with more abnormalities In 21 hemizygous patients in this study a short PR interval was present in four patients left ventricular hyper trophy in nine intraventricular conduction defects in four ST T changes in 18 sinoatrial and A V block in one each and left anterior hemiblock in one Only six hemizygous patients had normal ECG s whereas of 11 heterozygous patients five had normal ECG s ($p < 0.05$)

Since Fabry s disease may be amenable to therapy [1] it is essential to understand the natural history of electrical changes in the myocardium and the mechanisms thereto Our observations show that glycosphingolipid infiltration in the myocardium blood vessels and conduction system results in progression of conduction defects and chamber enlargement Occasionally decreases in electrical conduction time and regression of chamber enlargement patterns may also be apparent probably due to electrical alterations Not unexpectedly, hemizygosity is associated with more severe defects

Summary

Fabry s disease has been reported to be asso ciated with ECG abnormalities Thirty two patients with this disease followed in the Univer sity of Minnesota had ECG s and 15 had VCG s An abnormal rhythm was observed in two patients on initial examination and four developed abnormal rhythm on follow up exami nations A short PR interval (120 msec or less was seen in five patients Thirteen others had a PR interval that was less than 140 msec Conduc tion abnormalities involving the A V node or His bundle or its branches were present in 22 per cent of the patients most frequently the intraventric ular conduction defects progressing to the righ bundle branch block Atrial or ventricula enlargement was seen in 60 per cent of th patients left ventricular hypertrophy being th most common ST T changes with or withou chamber enlargement were seen in 10 patient One patient had an anterior myocardial infarc tion pattern on his ECG Hemizygosity was foun to be associated with significantly more abno malities than heterozygosity The severity conduction defects also increased with the dur tion of the disease process Vectorcardiography this study did not provide significant addition information other than that observed on the EC alone Since the pathology usually revea myocardial fibers conduction system and bloo vessels infiltrated with glycosphingolipid it believed that lipid infiltration is responsible f conduction defects chamber enlargement a other abnormalities Although Fabry s disease rare it may be amenable to therapy therefo recognition of cardiac involvement is importar

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REFERENCES

1 Sweeley C C Klionsky B Krivit W et al Fabr disease in Stanbury J B Wyngaarden J B Fredrickson O S editors The metabolic basis of inh ited disease ed 3 New York 1972 McGraw Hill Bo Company Inc pp 663 687
2 Ferrans V J Hibbs R G and Burda C D The he in Fabry s disease A histochemical and electron mic scopic study Am J Cardiol 26 95 1969
3 Roudebush C P Foerster J M and Bing O H L T

i our study we examined exercise induced changes only in patients with normal S T segments and T wave abnormalities not due to hypertrophy conduction disturbance or electrolyte imbalance The purpose of this study was to determine (1) the effect of T wave abnormalities at rest on the incidence of positive exercise tests in patients with and without ischemic heart disease (IHD) (2) the relation between exercise induced T wave changes and the ECG manifestations of ischemia and (3) the clinical significance of T wave normalization in the presence and absence of ischemic ECG abnormalities

Material and methods

In our institution an abnormal ECG at rest does not contraindicate an ECG stress test However we do not perform the ECG stress test for diagnosis of myocardial ischemia in the following patients (1) within 3 months after the onset of acute myocardial infarction (2) within 3 weeks after the administration of digoxin quinidine or procaine amide and 6 weeks after digitoxin (3) with ECG patterns of electrolyte imbalance and known abnormalities of plasma K or Ca concentrations (4) with horizontal or down sloping depression of the S T segment exceeding 0.5 mm in one or more of the following leads I II III aV_L, aV_F $V_{1\text{-}6}$

For this study we analyzed the records of all patients in whom an ECG stress test was performed during the period from 1963 to 1973 if their T wave at rest was isoelectric or negative in one or more of Leads I II V We excluded patients with the pattern of left ventricular hypertrophy (sum of amplitudes of S in V and R in $V_5 \geq 3.5$ mV) right ventricular hypertrophy (R/S ratio > 1 in $V_{1,2}$) incomplete right bundle branch block QRS duration greater than 0 10 sec., elevation of S T segment above the baseline and those treated with propranolol within a week before the test

A double (3 minutes) Master two step test standardized for age weight and sex was used in our laboratory until 1969 when we substituted a multistage treadmill test It had been our policy to repeat the Master two step test at a more rapid pace when the heart rate increase after the standard test appeared inadequate We excluded all patients who failed to achieve 85 per cent of the maximum predicted heart rate except those in

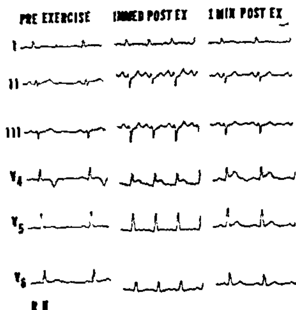


Fig 1 Example of a positive stress test manifested by elevation of ST segment and associated with complete T wave normalization ECG of a 60-year-old man with documented ischemic heart disease Before exercise T wave is negative in Leads V and V After exercise T wave is upright in all leads, and the QRS axis shifts superiorly Note that 1 minute after exercise T wave is upright in both Leads V and V but ST segment is elevated only in Lead V

whom the physician had interrupted the test because of ischemic changes in the monitored ECG (modified Lead V_5)

Our study included 185 patients with documented ischemic heart disease (IHD) (Group I) and 28 patients in whom IHD appeared unlikely (Group II) Group I included 162 men and 23 women Their average age was 52 years with a range of 27 to 77 years Of these patients 138 had had a documented transmural myocardial infarction within 2 years of the study and 47 had ≥ 85 per cent obstruction of at least one major coronary artery (18 of these 47 patients had had a myocardial infarction) Group II included 14 men and 14 women Their average age was 31 years with a range of 19 to 55 years Twelve of these 28 persons had normal coronary arteriograms The remaining 16 were men younger than 40 or women younger than 45 years without typical angina pectoris a major coronary risk factor i e, heredity hypertension diabetes mellitus hypercholesterolemia, and cigarette smoking or symptoms and signs of heart disease

In Group I a Master test was performed in 94 and a treadmill test in 91 patients and in Group

Electrocardiographic exercise test in patients with abnormal T waves at rest

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The use of the electrocardiographic (ECG) stress test in patients who have an abnormal ECG at rest has been impeded by the concern for patient safety and the difficulty in interpretation of the results The safety of the ECG stress test has been greatly enhanced by monitoring, and recent publications show that an abnormal ECG at rest does not contraindicate a monitored ECG stress test[1 6] even during early convalescence after acute myocardial infarction[7] However the significance of exercise induced changes in patients who have an abnormal ECG at rest has not been fully established[5 8]

One of the more common ECG changes at rest among patients in whom ECG stress test is needed for diagnostic purposes is the primary T wave abnormality One type of such abnormality persists frequently in patients with healed trans mural infarction, or nontransmural infarction and normal QRS duration, and another type rep resents a common "functional" repolarization abnormality in persons with chest pain of uncer tain etiology The difficulty in the interpretation of exercise induced ECG changes in patients with such T wave abnormalities may be attributed to two incompletely resolved problems (1) uncer tainty concerning the possible modification of the ischemic S T segment response by the concomi tant T wave change and (2) uncertainty con cerning the significance of exercise induced T wave normalization Of these two problems th second has received greater attention than th first

Master[1] considered the ECG test as positiv i e, indicative of myocardial ischemia, if negati T waves became positive and achieved an ampl tude of at least 1 5 mm Several examples of suc 'paradoxical' T wave changes have been pul lished in patients with documented ischem heart disease[9 11] However, more recent studi have challenged this interpretation Thus Ka tus[4] stated that reversal of T wave polarity ne the site of an old infarction cannot be regarded reliable evidence of myocardial ischemia In t study of Cohn and co workers[3] upright T wa developed after exercise in 10 patients in who the T waves were inverted before exercise Tl occurred in both the presence and the absence coronary artery disease and was not related to t development of ischemic S T abnormalities the study of Linhart and Turnoff,[6] reversal of wave from negative to positive occurred in patients and 34 of these had no coronary arte disease These two studies have shown that wave normalization after exercise can occur persons with or without coronary artery disea and that abnormalities of ventricular repolari tion at rest do not influence the incidence positive and negative responses to exercise Ho ever, these investigators did not focus specifica on primary T wave abnormalities and includ in their studies patients with abnormal S segments at rest[3 6] as well as patients receivi drugs which modify ventricular repolarizatio

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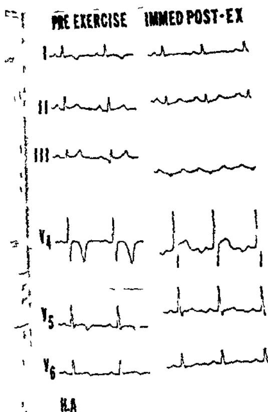


Fig 3 Example of a positive stress test manifested by elevation of the ST segment and U wave inversion and associated with complete T wave normalization ECG of a 44 year-old man with recurrence of angina pectoris following occlusion of a single aorta-coronary artery saphenous vein bypass graft Before exercise T wave is inverted in Leads V and V and biphasic in Lead V_6 After exercise T waves in these leads are upright ST segment is elevated only in Lead V and U wave is inverted in V and V

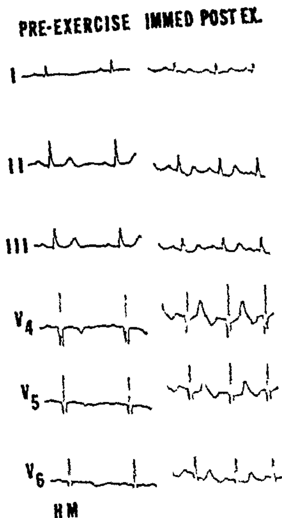


Fig 4 Example of a positive stress test manifested by depression of the ST segment and U wave inversion and associated with complete T wave normalization ECG of a 50-year old man 4 months after myocardial infarction Before exercise T wave is inverted in Leads V and V and biphasic in Lead V After exercise T wave in these leads is upright ST segment is depressed in Leads II III V V and V

not differ from each other in the incidence of myocardial infarction abnormal coronary arteriograms positive stress test or percentage of patients who failed to achieve 85 per cent of the predicted maximum heart rate We concluded that the results of both types of stress test could be combined

Table I shows that negative T waves before exercise occurred frequently in both groups in all six leads The abnormal T waves were more prevalent in all leads in patients without IHD

Change in T wave amplitude after exercise Fig 7 shows the magnitude of the maximum change in amplitude of the T waves in all leads in both groups of patients In the majority in both groups the T wave either did not change or became more positive or less negative in all leads In only less than 25 per cent of patients in both groups did the T wave become less positive or more negative This type of change occurred more frequently in patients with IHD than in those without and the difference between the two groups was significant ($p < 0.05$) in Leads I II III and V

The greatest increase in amplitude occurred in Leads V_4 and V_5 in both groups of patients Fig 7 shows that significant differences between the incidence of some types of T wave changes in two groups occurred in some leads but we could not detect a consistent trend in the pattern of these

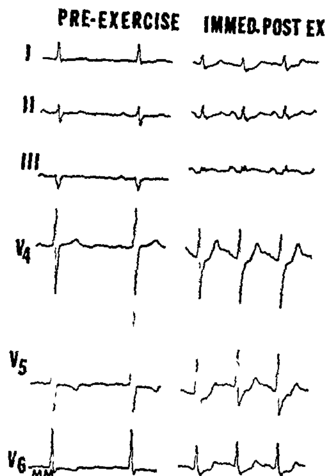


Fig 2 Example of a positive stress test manifested by depression of the ST segment and associated with complete T wave normalization ECG of a 64 year old woman with documented ischemic heart disease Before exercise T wave is negative in *Leads* V_4 and V_5 After exercise T wave in these leads is upright and *ST* segment is depressed

II, a Master test was performed in 15 and a treadmill test in 13 patients

Six standard leads (I II III V_4 V_5 and V_6) were recorded simultaneously with a multichannel direct writing recorder* on paper moving at 25 mm per second in the supine position at rest, immediately after exercise, and subsequently at 1 minute intervals until the heart rate and the ECG pattern returned to control The test was considered positive if one of the following changes appeared after exercise (1) horizontal or down sloping depression of the S T segment ≥ 0.1 mV,† (2) elevation of the S T segment above the baseline ≥ 0.1 mV,†[13] and (3) inversion of previously upright or isoelectric U wave[1]

Statistical significance was evaluated with the chi square test for comparing two proportions or Student's t test

*Elema Schonander
†Measured from *the level of* S T *segment* at rest

Table I Incidence of abnormal T wave in the ECG at rest

Lead	*Ischemic heart disease (185 patients)*		*Ischemic heart disease unlikely (28 patients)*	
	No	%	*No*	%
I	64	35	12	43
II	76	41	15	54
III	109	59	18	64
V_4	65	35	17	61
V_5	81	44	20	71
V_6	80	43	20	71

Table II Incidence of exercise induced T wave normalization

Lead	*Ischemic heart disease (185 patients)*		*Ischemic heart disease unlikely (28 patients)*	
	No	%	*No*	%
I	31/64	48	8/12	67
II	25/76	33	9/15	60
III	19/109	17	8/18	44
V_4	51/65	78	16/17	94
V_5	51/81	62	17/20	85
V_6	30/80	37	15/20	[illegible]
All leads†	50/185	27	16/28	57

Difference between groups is significant ($p < 0.0$[illegible])
†With abnormal T wave at rest

Results

The maximum heart rate after exercise in Group I averaged 133 ± 22 per minute and in Group II 154 ± 17 per minute These values were significantly different from each other ($p < 0.001$)

The stress test was positive in 162 of 185 patients in Group I and in one of 28 patients in Group II Fig 1 to 4 are examples of positive tests in Group I Fig 5 exemplifies a negative test in Group I and Fig 6 a negative test in Group II

We compared the characteristics of patients performing the Master two step test and those performing the treadmill test The ratio of patients performing a Master test to those performing a treadmill test was similar in both groups The average age and the ratio of men to women were similar in the performers of both tests in each of the two groups In Group I the Master test and the treadmill test performers did

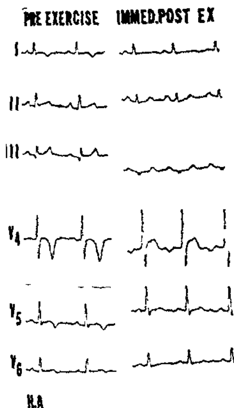


Fig 3 Example of a positive stress test manifested by elevation of the ST segment and U wave inversion and associated with complete T wave normalization ECG of a 44 year-old man with recurrence of angina pectoris following occlusion of a single aorta-coronary artery saphenous vein by pass graft Before exercise T wave is inverted in Leads V and V and biphasic in Lead V After exercise T waves in these leads are upright. ST segment is elevated only in Lead V and U wave is inverted in V and V

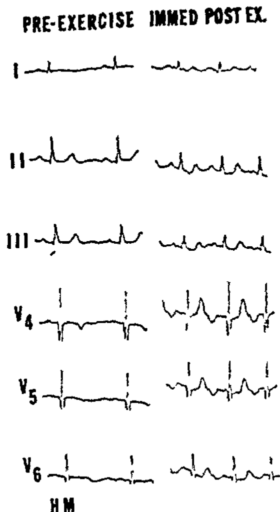


Fig 4 Example of a positive stress test manifested by depression of the ST segment and U wave inversion and associated with complete T wave normalization ECG of a 50-year-old man 4 months after myocardial infarction Before exercise T wave is inverted in Leads V and V and biphasic in Lead V After exercise T wave in these leads is upright ST segment is depressed in Leads II III V V_5, and V

not differ from each other in the incidence of myocardial infarction abnormal coronary ar teriograms positive stress test or percentage of patients who failed to achieve 85 per cent of the predicted maximum heart rate We concluded that the results of both types of stress test could be combined

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Change in T wave amplitude after exercise Fig 7 shows the magnitude of the maximum change in amplitude of the T waves in all leads in both groups of patients In the majority in both groups the T wave either did not change or be came more positive or less negative in all leads In only less than 25 per cent of patients in both groups did the T wave become less positive or more negative This type of change occurred more frequently in patients with IHD than in those without and the difference between the two groups was significant ($p < 0.05$) in Leads I II III and V_5

The greatest increase in amplitude occurred in Leads V and V_5 in both groups of patients Fig 7 shows that significant differences between the incidence of some types of T wave changes in two groups occurred in some leads but we could not detect a consistent trend in the pattern of these

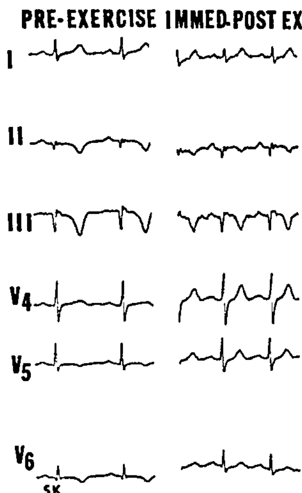


Fig 5 Example of a negative stress test associated with an incomplete T wave normalization ECG of a 62 year old man with documented but asymptomatic ischemic heart disease Before exercise T waves are inverted in Leads II III V and V After exercise T waves are upright in precordial leads but remain inverted in Leads II and III Note absence of ST segment or U wave changes after exercise

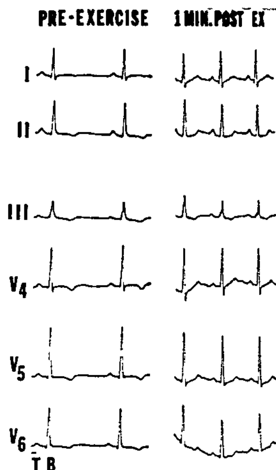


Fig 6 Example of a negative stress test associated with complete T wave normalization in a patient without ischemic heart disease ECG of a 25 year old man with chest pain not typical of angina pectoris and normal coronary arteriogram. Before exercise T waves are inverted in Leads II III V and V and flat in Lead I After exercise T waves are upright in all leads except Lead III Note absence of ST segment or U wave abnormalities after exercise

differences It appears therefore that the general pattern of exercise induced T wave changes is similar in patients with and without IHD

Exercise induced normalization of T wave Table II shows the incidence of exercise induced normalization of T waves In both groups T wave normalization occurred least frequently in Lead III and most frequently in Lead V Normalization occurred more frequently in patients without IHD than in those with IHD but the difference was significant only in Leads II III and V_6 Complete normalization i e normalization in all leads in which the T wave had been abnormal at rest,* occurred in 27 per cent of patients with IHD and 57 per cent of patients without ischemic heart disease

*Since negative T wave in Lead III at rest was not considered abnormal the designation of incomplete normalization does not exclude cases in which T wave in this lead remained negative after exercise

In Group I the test was positive in 45 of 50 (90 per cent) of patients with complete normalization and in 135 (87 per cent) of those with absent or incomplete normalization This difference was not significant Fig 8 shows that the same types of ischemic ECG changes occurred in the presence, or absence of complete T wave normalization Only in patients with a combination of a U wave inversion and deviation of the S T segment from the baseline (e g Fig 3), was the incidence of complete normalization significantly increased ($p < 0.01$) In patients with other types of ischemic changes (e g, Figs 1, 2 and 4) the difference between the presence and absence of complete normalization was not significant Our results show that the presence or absence of exercise induced T wave normalization does not separate patients with IHD from those without IHD

Increase in T wave amplitude An increase in

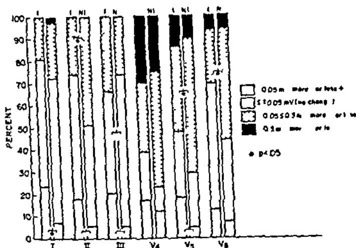


Fig 7 Distribution of exercise induced changes in T wave amplitude in 185 patients with documented IHD (I) and without evidence of IHD (NI) Dots mark the statistically significant differences between the neighboring columns connected by the brackets When the T waves became more positive or less negative (dotted and black bars) the polarity after exercise was positive in 5? per cent of cases in Lead III and in 83 to 100 per cent in five other leads. Discussion in text

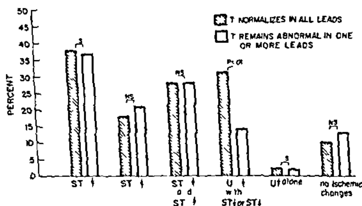


Fig. 8 Correlation between the presence and absence of complete T wave normalization and ECG manifestations of ischemia in 185 patients with IHD ST ↓ = depression of ST segment ST ↑ = elevation of ST segment U ↓ = U wave inversion See text

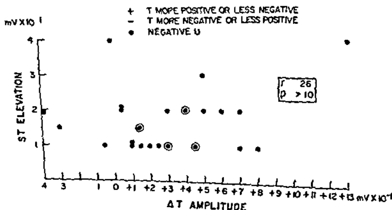


Fig 9 Maximum postexercise ST elevation and change in T amplitude in 23 patients (Lead V) See text

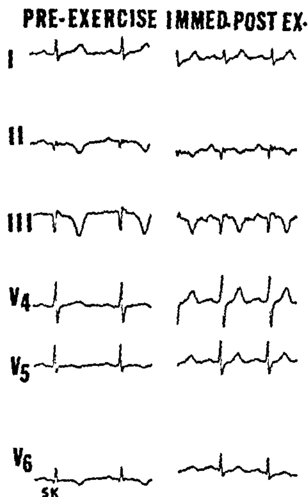


Fig 5 Example of a negative stress test associated with an incomplete T wave normalization ECG of a 62 year old man with documented but asymptomatic ischemic heart disease Before exercise T waves are inverted in Leads II III V and V After exercise T waves are upright in precordial leads but remain inverted in Leads II and III Note absence of ST segment or U wave changes after exercise

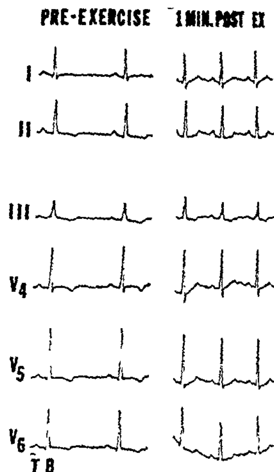


Fig 6 Example of a negative stress test associated with complete T wave normalization in a patient without ischemic heart disease ECG of a 25 year old man with chest pain not typical of angina pectoris and normal coronary arteriogram. Before exercise T waves are inverted in Leads II III V and V and flat in Lead I After exercise T waves are upright in all leads except Lead III Note absence of ST segment or U wave abnormalities after exercise

differences It appears therefore that the general pattern of exercise induced T wave changes is similar in patients with and without IHD

Exercise induced normalization of T wave Table II shows the incidence of exercise induced normalization of T waves In both groups T wave normalization occurred least frequently in Lead III and most frequently in Lead V Normalization occurred more frequently in patients without IHD than in those with IHD but the difference was significant only in Leads II III and V_6 Complete normalization, i e normalization in all leads in which the T wave had been abnormal at rest,* occurred in 27 per cent of patients with IHD and 57 per cent of patients without ischemic heart disease

*Since negative T wave in Lead III at rest was not considered abnormal the designation of incomplete normalization does not exclude cases in which T wave in this lead remained negative after exercise

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Increase in T wave amplitude An increase in

exercise induced elevation of S-T segment does not alter our results and conclusions

In our study the exercise test was positive only in 1 of 28 (4 per cent) patients who had no evidence of IHD In other studies of patients with abnormal ECG at rest and normal coronary arteriograms false positive tests occurred more frequently Thus in the study of Cohn and associates[3] the test was positive in nine of 23 patients while in two studies of Linhart and Turnoff the test was positive in four of 24 men and two of 19 women[4] who were not treated with drugs. The apparent lower incidence of false positive tests in our patients may be due to the exclusion of patients with pre existing depression of the S-T segment or to the younger age of our patients. There were no obvious differences in other variables which could have affected the incidence of false positive exercise tests namely the sex distribution and the maximum heart rate

Our results suggest that primary T wave abnormalities do not increase the incidence of false negative tests in patients with IHD or the incidence of false positive tests in persons without IHD Since the T wave abnormalities in patients with IHD were due predominantly to previous myocardial infarction and those in patients without IHD predominantly to functional disturbances of repolarization our results indicate that neither the postischemic" nor the functional primary T wave abnormalities alter the behavior of the S-T segment after exercise

Our study shows that the exercise induced T wave changes are similar in patients with and without IHD and do not differ from the exercise induced T wave changes in persons without heart disease who have a normal ECG at rest [5, 6]

Exercise induced T wave changes may be attributed to one or more mechanisms which are listed in Table III Although it may be difficult or impossible to determine the precise contribution of various mechanisms in each individual case we can draw the following general conclusions from our study (1) Changes secondary to the appearance of intraventricular conduction disturbances were uncommon In only two cases was a change from negative to positive T or an increase in the amplitude of positive T attributed to the widening of QRS associated with an appearance of more prominent S waves in the precordial leads (2) We did not observe the disappearance of secondary T wave changes after exercise because patients with such changes were excluded from this study (3) T waves became more negative or less positive in less than 25 per cent of patients The incidence of this response was greater in patients with IHD than in those without IHD This suggests that in certain patients the exercise induced increase in the magnitude of T wave inversion was due to the exacerbation of the primary postischemic T wave changes However a decrease in T wave amplitude may also be attributed to tachycardia induced decrease in the ventricular gradient (reference in Surawicz[17]) (4) T wave amplitude increased frequently in both patient groups particularly in the precordial leads Table III lists three possible mechanisms of exercise induced increase in the amplitude of positive T wave increased sympathetic stimulation (reference in Surawicz[17]) and exacerbation of either subendocardial or subepicardial ischemia pattern The results of our study favor the predominant role of increased sympathetic stimulation However in certain cases the specific effects of ischemia on the T wave amplitude were discernible e g in patients with depression S-T segment associated with U wave inversion (Fig 8)

The incidence of T wave normalization varied in different leads being lowest in Leads II and III and highest in Leads V_4 and V_5 Complete T wave normalization occurred more frequently in patients without IHD than in patients with IHD but the difference was significant in only three of six leads The frequent occurrence of complete T wave normalization in both patient groups is in keeping with the results of previous studies[3, 4] and suggests low specificity of this phenomenon Our study showed also that (1) complete T wave normalization was associated with a positive exercise test in 90 per cent of patients with IHD and with a negative test in all patients without IHD (2) in patients with IHD the incidence of positive tests was similar in the presence or absence of T wave normalization These results indicate that the exercise induced T wave changes are independent of the ECG manifestations of ischemia and that the behavior of primary T wave abnormalities after exercise does not alter the interpretation of the ischemic response The independent behavior of the S-T segment and T wave after exercise is not unexpected since the S-T segment and the T wave are generated by

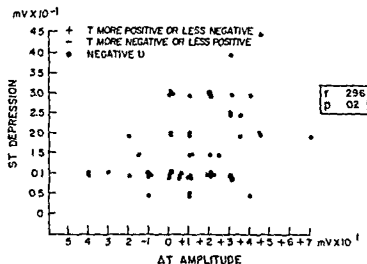


Fig 10 Maximum postexercise ST depression and change in T amplitude in 61 patients (Lead V) See text

Table III Postulated mechanisms and types of exercise induced changes in T wave amplitude, or polarity in Leads I to III and $V_{4\ 6}$

	Mechanism	*Expected T wave change*
1	Secondary to exercise induced intraventricular conduction disturbance	Direction opposite to vector of QRS component representing delayed activation
2	Secondary to regression of pre existing intraventricular conduction disturbance	Opposite to above
3	Exacerbation of post ischemic primary T wave changes	Less positive or more negative
4	Tachycardia induced decrease in ventricular gradient	Decreased amplitude
5	Sympathetic stimulation	Increased amplitude of positive less negative or normalization of negative
6	Subendocardial ischemia	Opposite to vector of S T segment
7	Subepicardial ischemia exacerbation of acute transmural infarction pattern or ventricular aneurysm pattern	Concordant with vector of S T segment

T wave amplitude occurred frequently in both patient groups (Fig 7) Since the ECG exercise test was positive in most patients with IHD and negative in most patients without IHD, the increase in T wave amplitude after exercise was related to the exercise rather than to the presence of myocardial ischemia However, it is well known that myocardial ischemia per se may contribute to an increase in T wave amplitude in the anterior precordial leads This may occur in both subendocardial ischemia with depressed S T segments (Fig 2), and subepicardial ischemia with elevated S T segments (Fig 1 and 3) It might have been predicted that changes in T wave amplitude induced by ischemia would correlate with the magnitude of S T deviation in a typical pattern of subepicardial ischemia and perhaps also in a typical pattern of subendocardial ischemia T wave changes due to factors other than ischemia would not be expected to correlate with the magnitude of S T deviation We, therefore, tested the possible correlation between exercise induced T wave changes and the deviation of the S T segment in Lead V_4 the lead which showed the greatest increase in T wave amplitude after exercise We found no correlation between maximum elevation of the S-T segment and change in T wave amplitude afte exercise in 23 patients ($r = 0\ 26$, $p > 0\ 1$) (Fig 9) and a weak correlation between maximum depression of the S T segment and increase in T wave amplitude after exercise in 61 patients ($r = 0\ 30$, $p = 0\ 02$) (Fig 10)

Discussion

Our criterion for the selection of patients into this study was the presence of an abnormal T wave at rest This method of selection results in patient material which differs from the cross section of patients undergoing diagnostic ECG exercise testing The patients in whom IHD was unlikely were usually in the younger age group the majority of patients with IHD had documented myocardial infarction Nevertheless the 88 per cent incidence of positive tests in our patients with IHD is comparable to the incidence of positive tests in the other two studies of patients with documented coronary artery disease and pre existing S T and T abnormalities Thus the test was positive in 74 of 87 (86 per cent) patients studied by Cohn and associates[5] and in 28 of 37 (76 per cent) patients not receiving drugs modifying the ECG response (Group II), studied by Linhart and Turnoff[6] We have included into the study patients with documented infarction in whom the S T segment became elevated after exercise Such S T segment elevation may not have the same clinical significance as the S T segment elevation in the absence of previous infarction However exclusion of patients with

Arterial thromboembolic complications in patients with Bjork Shiley and Lillehei-Kaster aortic disc valve prostheses

Jon Dale M D
Oslo Norway

Arterial thromboembolic complications represent a serious problem in patients with aortic ball valve prostheses.[1] The thrombi usually form on the valve itself and systemic embolism frequently occurs in the early and late course of valve replacement[1] while interference with the movement of the ball is less common[1] Anticoagulant treatment does not fully prevent these complications[1] although intense therapy has been found to offer some protection[2,3] The older Starr Edwards aortic ball valves were modified in order to reduce thromboembolism and a lower incidence has been found with the cloth covered valves by some[2,4] but not by others[3]

More recently aortic disc valves have been introduced These induce only a slight degree of intravascular hemolysis[4] as compared to the Starr Edwards valves[1] and lower systolic gradients have been reported in patients with the Bjork Shiley disc prosthesis[9] Satisfactory clinical results have been achieved by this valve type as well as by the Lillehei Kaster prosthesis

The thrombogenic properties of prosthetic valves are however a main determinant for valve selection and evaluation of thromboembolic complications is therefore important This investigation was performed in order to study the incidence and types of arterial thromboembolic complications in patients with aortic disc valves and to reveal factors that might influence the rate The aim was further to compare the incidence in patients with Bjork Shiley and Lillehei Kaster disc prostheses and finally to make a comparison with the results from a similar study in patients with Starr Edwards aortic ball valves.[2]

Materials and methods

The study comprises patients who received isolated aortic disc valves between December 1970 and November 1973 During this period such valves were implanted in 58 women and 138 men the mean age being 54 0 years and the range 15 to 72 years Advanced circulatory failure was not regarded as an absolute contraindication and 17 replacements were done as emergency operations because the patient s condition deteriorated rapidly

During these three years the operating team as well as the operative and postoperative treatment remained largely unchanged A disc oxygenator was employed the left coronary artery was always perfused and light hypothermia 32 to 34° C was routinely used Heparinization was achieved with 300 I U of heparin per kg body weight and after the operation the activity was neutralized with protamine Oral anticoagulation was started after two to four days

Two types of disc valves were used According to randomization performed by the surgical department 99 patients received a Bjork Shiley and 97 a Lillehei Kaster prosthesis. These two valves differ slightly in design The Bjork Shiley prosthesis has a free-floating tilting disc in a stellite cage with a sewing ring of Teflon[10] The disc opens 60 degrees and allows a central blood flow The cage consists of the ring and two bridges one on each side of the disc limiting its movements The prosthesis was introduced with a disc made of Delrin which was changed to one of

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different components of the ventricular action potential[18]

In Fig 1, 3, and 5 we have shown examples of ECG manifestations of ischemia, or T wave changes which appeared only in some of the simultaneously recorded leads Similar observations were made in several other cases They confirmed the diagnostic usefulness of the multiple lead system in the evaluation of the postexercise ECG changes[19]

Summary

The results of submaximal ECG exercise test were evaluated in six leads recorded simultaneously in two groups of patients with T wave abnormalities in one or more of Leads I, II, and V_{4-6} Group I included 185 patients with documented ischemic heart disease (IHD) and Group II 28 patients in whom IHD appeared unlikely The test was positive in 88 per cent of patients in Group I and in 4 per cent of patients in Group II In the majority of patients in both groups the T wave either did not change or became more positive or less negative after exercise The pattern of exercise induced T wave changes was similar in patients with and without IHD, and was influenced predominantly by the physiologic effects of exercise T wave normalization after exercise occurred frequently in patients with and without IHD, and in patients with positive and negative exercise tests Our results suggest that T wave abnormalities, not caused by hypertrophy, conduction disturbances drugs, or electrolyte imbalance do not modify the results of submaximal ECG stress test and that behavior of T wave after exercise does not alter the interpretation of the postexercise ECG The independent behavior of the S T segment and T wave after exercise is consistent with the theory that the S T segment and the T wave are generated by different components of the ventricular action potential

We acknowledge with gratitude the helpful editorial suggestions of Drs L S Gettes and R Shabetai

REFERENCES

1 Master A M The Master two step test Am Heart J 75 809 1968
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3 Cohn P R Vokonas P S Herman M V and Gorlin R Postexercise electrocardiogram in patients with abnormal resting electrocardiograms Circulation 43 648 1971
4 Kattus A A Exercise electrocardiography Recognition of the ischemic response false positive and negative patterns Am J Cardiol 33 21 1974
5 Froelicher V F Jr Yanowitz F G Thompson A J and Lancaster M C The correlation of coronary angiography and the electrocardiographic response to maximal treadmill testing in 76 asymptomatic men Circulation 48 597 1973
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9 Kalter H H Reversal to normal of abnormal resting electrocardiograms following exercise tolerance tests in patients with coronary artery sclerosis and angina pectoris N Y State J Med 53 1518 1953
10 Bourne G Paradoxical electrocardiogram in coronary exercise test Lancet 273 1320 1957
11 Dreifus L S Watanabe Y and Hermosillo A Electrocardiographic alterations in the presence of angina pectoris in Likoff W Segal B Insull W editors Atherosclerosis and coronary heart disease New York 1972 Grune & Stratton Inc p 243
12 Doan A E Peterson D R Blackmon J R and Bruce R A Myocardial ischemia after maximal exercise in healthy men Am Heart J 69 11 1965
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15 Lepeschkin E and Surawicz B Characteristics of true positive and false positive results of electrocardiographic Master two step test N Engl J Med 258 511 1958
16 Berkson D M Stamler J and Jackson W The precordial electrocardiogram during and after strenuous exercise Am J Cardiol 18 43 1966
17 Surawicz B The pathogenesis and clinical significance of primary T wave abnormalities in Schlant R C and Hurst J W editors Advances in electrocardiography New York 1972 Grune & Stratton Inc p 397
18 Harumi K Burgess M J and Abildskov J A A theoretic model of the T wave Circulation 34 657 1966
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Artenal thromboembolic complications in patients with Bjork-Shiley and Lillehei Kaster aortic disc valve prostheses

Jon Dale M D
Oslo Norway

Artenal thromboembolic complications represent a serious problem in patients with aortic ball valve prostheses [1] The thrombi usually form on the valve itself and systemic embolism frequently occurs in the early and late course of valve replacement [1] while interference with the movement of the ball is less common Anticoagulant treatment does not fully prevent these complications [2] although intense therapy has been found to offer some protection [3, 5] The older Starr Edwards aortic ball valves were modified in order to reduce thromboembolism and a lower incidence has been found with the cloth covered valves by some[2, 5] but not by others [3]

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19 Mason R E Likar I Biern R O., and Ross R S Multiple lead exercise electrocardiography Circulation **36** 517 1967

or considerable permanent functional disturbance intermediate were those that produced more moderate symptoms lasting for at least two weeks while mild were episodes with slight and transient symptoms

Results

The groups of patients with the two valve types were well comparable with regard to age at operation prevalence of continuous arrhythmia and concomitant mitral valve disease not considered serious enough to require mitral valve implantation number of emergency operations and mean heart size while a difference appeared in sex distribution (Table I)

The mortality rate at operation and during the first postoperative month was 16 3 per cent (Table II) Three of the 32 early deaths were caused by arterial thromboembolic complications (Table III) A 62 year old woman had her previously implanted ball valve replaced by a Lillehei Kaster valve because of paravalvular leakage She died after seven days and autopsy revealed multiple embolic cerebral infarctions Two men died from myocardial infarction one two days and the other ten days after implantation of Bjork Shiley prostheses In both autopsy disclosed that coronary thrombi were the cause of death while atherosclerosis was minimal.

Four of the eight early thromboembolic complications occurred in each valve group Six of these complications were diagnosed within one week after operation

The average observation time for the patients who survived the postoperative period was 23 5 months as calculated from the beginning of the second month (Table IV) Two of the patients had their Bjork Shiley valves replaced by Lillehei Kaster prostheses and both were included in each of the groups accordingly The total observation time was quite similar in the two valve groups Only twelve late deaths occurred the total number of patients who died being 44 22 with each of the valve types

A total of 19 late arterial thromboembolic complications were observed in 18 patients and three of them died (Table V) Thus 11 6 per cent of the patients suffered such late complications and 25 per cent of the late deaths were caused by arterial thromboembolism

Ten episodes of cerebral embolism were recorded and the death of a 57 year old man 18 months after the implantation of a Lillehei Kaster valve was thought to be caused by a cerebral embolus but unfortunately autopsy was not performed

Of great importance were thrombi that formed on the valve and limited the movement of the disc since this seriously affected the condition of the patients Four patients suffered thrombotic valve malfunction in two of them the complication remained undiagnosed and they died in other hospitals both had Bjork Shiley valves Two patients survived because the thrombi were removed by operation one with each valve type In all four circulatory failure developed and the complications appeared from three to 13 months after the valve implantation. Two of the patients had atrial fibrillation and mitral valve disease In the two who died from valve malfunction anticoagulant therapy had been adequate while it was unsatisfactory in periods in the third with a Bjork Shiley prosthesis In the only patient with thrombotic malfunction of a Lillehei Kaster valve the anticoagulant treatment had been

Table IV Observation time in patients with single aortic disc valves the first postoperative month not being included Two patients belong to both groups because their Bjork Shiley valves were replaced by Lillehei Kaster prostheses

Valve type	*No of valves*	*Observation time (months)*	
		Total	*Mean*
Bjork-Shiley	81	1,943	24 0
Lillehei Kaster	85	1,963	23.1
Combined	166	3,906	23.5

Table V Late arterial thromboembolic complications in patients with aortic disc valve prostheses

Thromboembolic complications	*No of complications*	*No of patients*	*No of Deaths*
Cerebral emboli	10	9	1
Serious	1		
Intermediate	4		
Mild	5		
Peripheral emboli	1	1	
Retinal emboli	3	3	
Myocardial infarction	1	1	
Valve malfunction	4	4	2
Total	19	18	3

Table I Comparison of the two groups of patients who received either a Bjork Shiley or a Lillehei Kaster aortic disc valve according to randomization

	Groups of patients with valve type		
	Bjork Shiley	*Lillehei Kaster*	*Combined*
Number of patients	99	97	196
Number of men	62	76	138
Number of women	37	21	58
Mean age at operation (years)	54 6	53 3	54 0
Mean heart size (ml per sq M)	596	634	614
Emergency implantations	7	10	17
Patients with arrhythmia	7	11	18
Patients with mitral disease	18	18	36
Patients with coronary disease	11	13	24

Table II Mortality after implantation of single aortic disc valves

	Number of patients with valve type		
	Bjork Shiley	*Lillehei Kaster*	*Combined*
Valve implantations	99	97	196
Early deaths	18	14	32
Alive after one month	81	83	164
Late deaths	4	8	12
Alive at follow up	77	75	152

Table III Arterial thromboembolic complications during the first month after aortic disc valve implantation

Type of complication	*No of complications*	*No of deaths*
Cerebral emboli	3	1
Peripheral emboli	1	
Myocardial infarction	4	2
Total	8	3

Pyrolite carbon in 1971 [14] The Lillehei Kaster valve incorporates a free floating Pyrolite carbon disc within a titanium annular housing The disc is permitted to open 80 degrees allowing a central blood flow [15] The movement of the disc is stopped by two short horns on the aortic side of the ring, which is encircled by porous Teflon for sewing

Follow up

Most of the patients were submitted to the cardiologic department one year after the valve implantation and their hospital records were examined Reports have been obtained from other hospitals or physicians concerning patients who have died since the operation

A request was sent to all surviving patients to meet for examination between September 1974 and March 1975, and all except six reported A careful history with special emphasis on thromboembolic or bleeding complications was obtained A physical examination was performed and ECG as well as x ray of heart and lungs was included Blood samples were analyzed with regard to platelet function coagulation and intravascular hemolysis but the results will be published separately

The intensity of the anticoagulant therapy was controlled by Thrombotest (TT) [16] in which the therapeutic range was considered to lie between 5 and 15 per cent of normal activity

A questionnaire was sent to all patients physicians asking for additional information and their relatives were contacted when necessary Thus the data presented were obtained from three different sources hospital records, examination of the patients and information from doctors or relatives None of the patients were lost for follow up

Arterial thromboembolic complications were diagnosed according to the following criteria (1) Acute onset (2) Neurological signs in cerebral embolism or functional disturbance due to arrested blood flow in other regions (3) Observation of the symptoms by others than the patient (4) Duration of symptoms for more than half an hour Myocardial infarction was diagnosed from a history of precordial pain ECG findings and rise of temperature leukocyte counts or transaminases Thrombus on the valve was listed as a complication only when the function of the valve was disturbed, and when the thrombus was demonstrated at operation or autopsy Systemic emboli could also be diagnosed by direct demonstration of the embolus

Cerebral emboli were divided in three subgroups serious' were emboli that caused death

their doctors were asked for information regarding anticoagulant therapy and reports were received comprising two thirds of the patients According to this the TT values were regularly maintained within therapeutic limits in 88 per cent of the patients

Continuous arrhythmia mostly atrial fibrillation existed in three patients who suffered late thromboembolic episodes (16 7 per cent) and in 10 of those who did not (6 9 per cent) while the incidence of transient arrhythmias was unknown Concomitant mitral disease not serious enough to require mitral valve implantation was diagnosed in two (11 1 per cent) patients with late thromboembolism and in 31 (21 2 per cent) of those *without* The mean heart size in the same groups at follow up was 598 and 564 ml per square meter respectively None of the differences were statistically significant

Bleeding complications were infrequent One man died postoperatively from a subdural hematoma he had been in coma since the second day after operation Intracranial bleeding was not seen in the late course of valve replacement Five episodes of gastrointestinal bleeding occurred in four patients two after self medication with large doses of acetylsalicylic acid while transient hematuria was seen once The TT values that were known before four of the episodes were all in the therapeutic range

Discussion

A previous study from this hospital revealed that early arterial thromboembolic complications occurred frequently after aortic ball valve implantation and myocardial infarction caused several deaths The present investigation demonstrates that postoperative arterial thromboembolism often develops also after disc valve implantation This indicates that the early formation of arterial thrombi is more influenced by the surgical procedure extracorporeal circulation or postoperative treatment than by the design of the implanted valve The mechanisms behind the strong tendency to postoperative arterial thrombosis are complex Predisposing factors are probably the foreign material represented by the valve itself turbulence caused by the valve intravascular hemolysis with liberation of platelet aggregating substances as adenosine diphosphate (ADP) from red cells damage of the intima[3] with exposure of thrombogenic subintimal tissue[12] and finally development of thrombocytosis with young and reactive platelets some days after the operation[13]

The results presented clearly demonstrate that late arterial thromboembolism is a serious problem also after aortic disc valve implantation The incidence has not been evaluated by others and few reports have been published concerning such complications in disc valve patients altogether Bjork and co workers[1] observed 10 episodes in 160 patients with Bjork Shiley valves most of the complications occurring in patients not taking anticoagulants In another study[2] seven out of 121 patients suffered massive thrombosis on their Bjork Shiley valves which limited the movements of the discs and caused five deaths Only two of the seven patients received anticoagulants while in the present series the majority of thromboemboli occurred in patients with adequate anticoagulant treatment

The incidence of late arterial thromboembolic complications was not lower in patients with disc valves than in those with Starr Edwards aortic ball valves of series 2 300 previously used in this hospital[2] In the patients with this ball valve type 4 0 complications occurred per 100 patients per year Although these ball valves were implanted on average two years before the disc prostheses a rough comparison seemed justified Thus the patient groups were well comparable[2] the operating technique and team of surgeons as well as the postoperative treatment was largely the same the anticoagulant treatment was equally intense and finally the follow up was done in exactly the same way The results therefore strongly indicate that the introduction of aortic disc valves instead of cloth covered ball valves has not reduced the problem of arterial thromboembolism

An important difference in the types of thromboembolic complications between patients with ball valves and disc valves was indicated Thus thrombi that affect the functions of the valve itself represent a serious problem in patients with aortic disc prostheses while this complication was not seen in the late course of ball valve replacement in our studies[2, 5] and has rarely been found by others[7] The tendency toward thrombosis disturbing the disc valves may partly be due to the hemodynamic properties of the prostheses partly to the fact that the tilting of

Table VI The incidence of late arterial thromboembolic complications in relation to aortic disc valve type and to time since the implantation Episodes during the first postoperative month are not included

	Number of complications	*Complications per 100 patients per year*
Valve type		
Bjork Shiley	9	5 6
Lillehei Kaster	10	6 1
Combined	19	5 9
Time since operation		
Within first year	8	5 3
One to two years	8	6 9
After two years	3	5 1

Table VII Distribution of Thrombotest (TT) values before arterial thromboembolic complications and at the follow up examination in patients receiving anticoagulant therapy

	Distribution of TT values in per cent			
		In valve groups at follow up		
TT value	*Before thrombo emboli*	*Bjork Shiley*	*Lillehei Kaster*	*Combined*
5 to 10 per cent	58 8	30 4	22 1	26 3
11 to 15 per cent	17 6	26 1	44 1	35 0
16 to 20 per cent	17 6	24 6	13 2	18 9
21 to 25 per cent	0	11 6	10 3	11 0
Higher than 26 per cent	5 9	7 3	10 3	8 8

discontinued early after the implantation for unknown reasons

In both patients who died a white platelet-fibrin thrombus was attached to the aortic side of the disc In one, the thrombus was also adherent to the aortic wall, thereby inhibiting any movement of the disc completely In the other, the mobility of the disc was considerably reduced and embolic occlusion of a femoral and renal artery was found as well Reoperation of the third patient with a malfunctioning Bjork Shiley valve disclosed a worm shaped thrombus on the metallic parts of the cage protruding through the lesser orifice and fixing the disc in a semi open position In the patient with dysfunction of a Lillehei Kaster prosthesis operation revealed an elongated platelet-fibrin thrombus that extended from its attachment on the aortic side of the disc through the smallest aperture preventing closure of the valve

Arterial thromboembolism developed in two of the three patients who did not receive anticoagulant therapy A cerebral embolic episode occurred in a patient two months after withdrawal of anticoagulant treatment because of repeated gastrointestinal bleeding while another who refused to take anticoagulants remained free of complications

The total incidence of arterial thromboembolic complications was 5 9 episodes per 100 patients per year (Table VI) and they were quite equally distributed between the two valve groups The occurrence of the complications seemed not to be dependent upon time since operation but only 706 'patient months were recorded after more than two years

Considering the Bjork Shiley prostheses four late complications developed in patients with Delrin discs and five in those with discs made of Pyrolite carbon the incidence being 4 5 and 6 9 respectively The difference is not statistically significant One patient with each disc type died from valve malfunction

Disregarding the patients not given anticoagulants eight late arterial thromboembolic complications developed in those with Bjork Shiley valves while nine embolic episodes were diagnosed in patients with Lillehei Kaster prostheses Thus, the incidence in patients receiving anticoagulant therapy was 5 0 episodes per 100 patients per year in the Bjork Shiley group and 5 6 in those with Lillehei Kaster valves the combined incidence being 5 3 The intensity of the anticoagulant treatment at the time of thromboembolic complications was satisfactory, since 76 per cent of the TT values preceding the episodes were in the therapeutic range as compared to 61 per cent of all values at the end of the follow up (Table VII) Thus adequate anticoagulant therapy did not fully prevent thrombus formation The intensity of the treatment differed only slightly between the groups of patients with the two valve types However the follow up examination disturbed the daily routine of the patients and the TT values obtained could deviate from their usual levels Therefore

Bjork Shiley or Lillehei Kaster aortic disc valve implanted Eight patients suffered from such complications in the course of the first postoperative month and three of them died two from myocardial infarction and one from cerebral embolism

Nineteen late thromboembolic complications developed in 18 of the 164 patients who survived the postoperative period the incidence being 5 9 episodes per 100 patients per year The two valve types were found to be equally thrombogenic and the rate was not lower than that in patients with Starr Edwards aortic ball valves of series 2 300 previously studied Particularly serious was valve malfunction caused by thrombi that limited the movement of the discs Early recognition of this condition is essential because the only effective therapy is removal of the thrombus Three patients with a Bjork Shiley and one with a Lillehei Kaster valve suffered this complication and two died while cerebral embolism caused a third late death Two of the three patients who had not received anticoagulants developed thromboembolic complications while most episodes occurred in spite of well maintained anticoagulant treatment

It is concluded that arterial thromboembolic complications remain a considerable problem also after aortic disc valve implantation and that thrombotic valve malfunction is particularly serious and requires special attention

The cooperation of Prof Dr O Storstein Medical Department B and of Prof D K V Hall Surgical Department A is greatly appreciated I am also indebted to Mrs A L Almaas for skilled technical assistance

REFERENCES

1 Cleland J and Molloy P J Thromboembolic omplications of the cloth covered Starr Edwards prostheses no 2,300 aortic and 6 300 mitral, Thorax 28 41 1973
2 Dale J Arterial thromboembolic complications in patients with Starr Edwards aortic ball valve prostheses AM HEART J 91 653 1976
3 Barnhorst D A Oxman H A Connolly D C Pluth J R Danielson G K Wallace R B and McGoon D C Isolated replacement of the aortic valve with the Starr Edwards prosthesis J Thorac Cardiovasc. Surg 70 113 1975
4 Spencer F C Reed G E Clauss R H Tice D A and Reppert E H Cloth-covered aortic and mitral valve prostheses, J Thorac Cardiovasc Surg 59 97 1970
5 Friedli B Aerichide N Grondin P and Campeau L Thromboembolic complications of heart valve prostheses, AM HEART J 81 02, 1971
6 Duvoisin G F Wallace R B Ellis F H Anderson M W and McGoon D C Late results of cardiac valve replacement, Circulation 37 and 38(Suppl. 2) 75 1968
7 Akbarian M Austen W G., Yurchak P M., and Scannell, J C Thromboembolic complications of prosthetic cardiac valves Circulation 37 826 1968.
8 Matloff J M Collins, J J Sullivan J M Gorlin R and Harken D Control of thromboembolism from prosthetic heart valves, Ann Thorac Surg 8 133 1969
9 Hodam R Starr A Raible D and Griswold H Totally cloth-covered prostheses. A review of two years clinical experience Circulation 41 and 42(Suppl. 2) 33 1970
10 Bjork V O., Olin C., and Rodriguez L. Comparative results of aortic valve replacement with different prosthetic heart valves J Cardiovasc Surg 13 268 1972.
11 Kaster R L. Lillehei, C W., and Starek P J K The Lillehei Kaster pivoting disc aortic prosthesis and a comparative study of its pulsatile flow characteristics with four other prostheses, Trans. Am Soc Artif Intern Organs 16 233 1970
12 Nitter Hauge S Sommerfelt, S C., Hall, K V., Froysaker T and Efskind, L. Chronic intravascular hemolysis after aortic disc valve replacement Comparative study between Lillehei Kaster and Bjork-Shiley disc valve prostheses Br Heart J 36 781 1974
13 Myhre E Dale J., and Rasmussen K Erythrocyte destruction in different types of Starr Edwards aortic ball valves, Circulation 42 515 1970
14 Bjork V O Henze A. and Holmgren A Five years experience with the Bjork Shiley tilting disc valve in isolated aortic valvular disease J Cardiovasc Surg 16 451 1975
15 Nitter Hauge S Hall K V., Froysaker T and Efskind, L. Aortic valve replacement One-year results with Lillehei Kaster and Bjork Shiley disc prosthesis, AM HEART J 88 23 1974
16 Owren P A Thrombotest A new method for controlling anticoagulant therapy Lancet 2 754 1959
17 Salzman E W., Berger S Merrill, E W., and Wong, P S L. Thrombosis induced by artificial surfaces Thromb Diath Haemorrh Suppl. 59 107 1974
18 Stein P D., and Sabbah, H N Measured turbulence and its effect on thrombus formation Circ Res. 35 608 1974
19 Holmsen H The platelet its membrane physiology and biochemistry Clin Haematol. 1 235 1972
20 Hovig T The ultrastructure of blood platelets in normal and abnormal states. Ser Haematol. 1 3 1968.
21 Storstein O Efskind, L., and Torgersen O The mechanism of myocardial infarction following prosthetic aortic valve replacement Acta Med. Scand 193 103 1973
22 Baumgartner H R Platelet interaction with vascular structures Thromb Diath Haemorrh. Suppl. 51 161 1972.
23 McKenzie F N Dhall D P., Arfors K E., Nordlund S and Matheson N A. Blood platelet behaviour during and after open heart surgery Br Med J 2 795 1969
24 Ben Zvi, J., Hildner F J., Chandraratna P A., and Samet P Thrombosis on Bjork Shiley aortic valve prosthesis Am. J Cardiol 34 538 1974
25 Dale J Myhre E., Storstein O Stormorken H and Efskind L. Prevention of arterial thromboembolism with acetylsalicylic acid A controlled clinical study in patients with aortic ball valves AM HEART J (In press)
26 Kloster F E., Herr R H Starr A., and Griswold H E Hemodynamic evaluation of a cloth-covered Starr Edwards valve prosthesis Circulation 39 and 40(Suppl. 1) 119 1969
2 Roberts, W C Fishbein M C., and Golden A Cardiac

the discs is more easily affected by thrombi than the movements of the balls The Starr Edwards ball valves of series 2,300 with its double cloth covering of the ring and stellite ball has a small orifice-to-ball ratio with high systolic gradients across the valve [3] The disc valves allow a wider opening and the Bjork Shiley prosthesis has been found to offer less resistance towards the blood stream especially after exercise [10] However the discs themselves probably cause considerable turbulence on their aortic side and turbulent flow favors thrombus formation [18] which would contribute to the tendency towards thrombosis on disc valves [4, 7]

The two disc valve types used appeared to be equally thrombogenic and the change of disc material in the Bjork Shiley prosthesis did not seem to reduce the tendency to thrombus formation The results suggest, however, a difference in the liability for functional disturbance between the two valve types used, since the only valve complication in the Lillehei Kaster group developed in a patient not taking anticoagulants although definite conclusions cannot be drawn This investigation confirms the strong tendency towards thrombotic affection of Bjork Shiley valves already reported [4] The metallic parts of the cage differ between the two valve types [10, 11] which might be of importance with regard to thrombotic malfunction

It is of vital importance to reveal thrombi that interfere with valve function since the only effective treatment is surgical removal Most typical auscultatory findings are systolic or diastolic murmurs caused by defective opening or closure of the valve, and absence of the closing click [24] The clinical diagnosis is usually difficult however, and thrombus on the valve should always be suspected when the patient s condition deteriorates

Anticoagulants have been found to offer some protection against arterial thromboembolism in patients with ball valves,[3, 5, 8] which indicates a role of coagulation in the development of arterial thrombi However anticoagulant therapy cannot be expected to prevent arterial thrombus formation completely, because it does not inhibit platelet aggregation which is an important step in arterial thrombosis [28] This explains the occurrence of thromboembolic complications in spite of satisfactory anticoagulation A promising approach in the prophylaxis of arterial thromboembolism in patients with prosthetic valves is the combination of drugs that influence both platelet function and coagulation [25, 9] No prophylaxis is on the contrary probably associated with a particularly high risk of thromboembolic complications [14, 24] Anticoagulant therapy must therefore be strongly recommended either alone or in combination with drugs that inhibit platelet function

Concomitant mitral disease and constant arrhythmia might increase the risk of thromboembolism As in ball valve patients [2] however such influence was not found, possibly because of the anticoagulant therapy

The incidence of thromboembolic episodes has been claimed to be lowered by time after ball valve implantations [3, 7] This is not supported by previous studies from this hospital [2, 5] and no decline was found in the present material The observation time is however, too short to allow conclusion for more than the two first years

The development of late arterial thromboembolism is not mainly determined by the degree of intravascular hemolysis, because such complications were equally frequent in the disc valve patients as in those with Starr Edwards valves of series 2 300 [2] in spite of considerably less hemolysis [12, 13] The important factors triggering thrombosis are most probably the foreign material of the valve its design, and the turbulence provoked

Intense anticoagulant therapy could induce bleeding and intracranial bleeding is not uncommon in ball valve patients [1, 5, 7, 30, 33] Their disturbed platelet function[34] might contribute to this tendency Several cases of fatal bleeding have been reported in disc valve patients receiving anticoagulants [14, 35] while serious bleeding was not observed in this study The low incidence of hemorrhagic complications is most probably related to the satisfactory anticoagulant treatment in the majority of the patients

The present study demonstrates that arterial thromboembolic complications particularly valve malfunction, constitute a serious problem after aortic disc valve implantation and that the late incidence is not lower than with cloth covered aortic ball valves

Summary

Arterial thromboembolic complications were studied in 196 patients who had either a single

Significance and treatment of nocturnal angina preceding myocardial infarction

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Angina which disturbs sleep is termed nocturnal angina and may be the presenting manifestation of coronary heart disease[1] Previous discussions of this entity have suggested different mechanisms which include association with dreaming[2] decreased blood pressure and early congestive heart failure

In this study we compare various characteristics of patients with and without nocturnal angina and discuss its probable etiology These characteristics include location of infarction prior congestive heart failure and cardiomegaly

Method

A total of 174 consecutive patients with acute myocardial infarction (MI) were evaluated in our coronary care unit The diagnosis of acute transmural MI was based on the presence of a history of typical precordial pain the development of significant Q waves and the typical evolution of serum enzymes Anterior wall MI included both anteroseptal and anterolateral inferior wall MI included inferoposterior and inferolateral MI Those patients with a typical history and serial enzyme elevations consistent with acute MI but without the evolution of significant Q waves were diagnosed as having subendocardial infarction

At the time of admission a questionnaire was completed concerning the characteristics of the patient s pain and the patient s symptoms within the month prior to admission This evaluation included questions concerning angina on exertion nocturnal angina and clinical symptoms of congestive heart failure Nocturnal angina was defined as anginal pain which aroused a patient from sleep and was usually similar to the daytime chest pain A history of clinical congestive heart failure was defined as dyspnea on exertion orthopnea or paroxysmal nocturnal dyspnea in the absence of any apparent noncardiac cause Cardiomegaly was evaluated radiographically at the time of admission and was judged to be present if the cardiothoracic ratio was greater than 0 50

P values were obtained by chi square statistical analysis

Results

Of the 164 patients studied 104 (63%) had angina during the month prior to myocardial infarction This included 23 (13 per cent) patients who experienced nocturnal angina The incidence of nocturnal angina was significantly higher in those with anterior MI ($p < 0\ 005$) and subendocardial infarction ($p < 0\ 02$) than in patients with inferior MI (Fig 1)

The group with nocturnal angina was comprised of 16 men and seven women with an average age of 58 years the group without nocturnal angina was comprised of 89 male and 43 female patients with an average age of 61 years Congestive heart failure in the month prior to admission was more common in those with nocturnal angina (9/23) than in those without (3/141) ($p < 0\ 001$) Cardiomegaly was seen in

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pathology after valve replacement by disc prosthesis Am J Cardiol 35 740 1975
28 Mustard J F Kinlough Rathbone R L and Packham M A Recent status of research in the pathogenesis of thrombosis Thromb Diath Haemorrh Suppl 59 157 1974
29 Sullivan J M Harker D E and Gorlin R Pharmacologic control of thromboembolic complications of cardiac valve replacement N Engl J Med 284 1391 1971
30 Reed G E Clauss R H Tice D A and Acinpura A J Five year experience with Magovern aortic prostheses Circulation 43 and 44(Suppl 1) 73 1971
31 Gadboys H L Litwak R S Niemetz, J and Wisch N Role of anticoagulants in preventing embolization from prosthetic heart valves J A M A 202 ?8? 1967
32 Beall A C Bloodwell R D Bricker D L Okies J E Colley D A and DeBakey M E Prosthetic replacement of cardiac valves Am J Cardiol 23 ?50 1969
33 Bryant L R Trinkle J K Spencer F C Danielson G K Shabetai R and Reeves J T Cardiac valve replacement Results in patients with advanced disability J A M A 216 996 1971
34 Dale J and Myhre E Platelet function in patients with aortic ball valves AM HEART J (In press)
35 Stalpaert G Suy R Daenen W Detournay G and De Wulf C Experience with the Bjork Shiley valvular replacement J Cardiovasc Surg 14 542 1973

could be due to decreased perfusion beyond a stenosed coronary artery cannot be excluded

Comparisons of anterior and inferior transmural MI have shown a higher mortality rate[8] and more left ventricular dysfunction in those with anterior wall involvement reflecting more extensive myocardial damage. This is explained by the coronary artery anatomy and its relationship to location of infarction. Although some variation exists, a greater proportion of the left ventricle is usually infarcted with occlusion of the left anterior descending coronary artery, and significant disease of this vessel has been found in 96 per cent of patients with anterior myocardial infarction. Disease of the right coronary artery, which was noted in 87 per cent of those with inferior MI, may lead to less myocardial necrosis.

Hamby and associates[1] noted that a history of congestive heart failure and cardiomegaly was more common in patients with anterior MI than in patients with a normal QRS or inferior MI. They also noted that the group with multiple infarctions had abnormal hemodynamics, which would explain the occurrence of nocturnal angina in six of our patients with subendocardial infarction, all of whom had previous infarctions.

We believe that the increased myocardial oxygen demand associated with decreased ventricular function and ventricular dilatation is the most likely cause of nocturnal angina. This is based on our observation that nocturnal angina was much more common preceding anterior MI farction and was associated frequently with congestive heart failure prior to admission and cardiomegaly.

It is of interest to note that three of the four patients with nocturnal angina associated with dreaming reported by Nowlin and associates were studied and all found to have significant two or three vessel disease. Their case No. 3 progressed to congestive heart failure requiring digitalis after the nocturnal angina subsided.

With this probable mechanism in mind the treatment of nocturnal angina may differ from that of effort angina. Digitalis has been found to improve ventricular function and not aggravate symptoms in patients with uncomplicated angina[2] and is suggested in the treatment of nocturnal angina. Propranolol, which has been mentioned in the treatment of nocturnal angina,[11] should be used with great care and probably in combination with digitalis. This combined therapy has been recommended[11] in patients with large hearts in order to prevent further increase in heart size by propranolol.

We conclude that the presence of nocturnal angina in those who develop MI increases the likelihood that the infarction will be either anterior or subendocardial rather than inferior. The association of nocturnal angina and congestive heart failure to anterior MI is probably due to more severe and probably significant left coronary artery disease in patients having nocturnal angina. In addition to routine treatment of heart failure with salt restriction, diuretics, and digitalis, propranolol should be used with caution and consideration given to early coronary angiography. Bypass surgery may prove beneficial in those patients with good ventricular function.

Summary

The presence of nocturnal angina and congestive heart failure within the month prior to admission was evaluated in the 174 patients with acute myocardial infarction. Heart size was evaluated radiographically at the time of admission. Twenty-three patients (13 per cent) experienced nocturnal angina. The incidence of nocturnal angina was significantly higher in those with anterior myocardial infarction ($p < 0.005$) and subendocardial infarction ($p < 0.02$) when compared with patients with inferior MI. Congestive heart failure was more common prior to admission in those with nocturnal angina (9/23) as opposed to those without (3/141) ($p < 0.001$). Cardiomegaly was seen in 9/23 patients with nocturnal angina and 22/141 without ($p < 0.02$).

We conclude that the presence of nocturnal angina in those who develop MI increases the likelihood that the infarction will be either anterior or subendocardial rather than inferior. The association of nocturnal angina and congestive heart failure to anterior myocardial infarction is probably due to more severe and probably significant left coronary artery disease.

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REFERENCES

1. Gorlin R: Pathophysiology of cardiac pain. Circulation 32:138, 196.

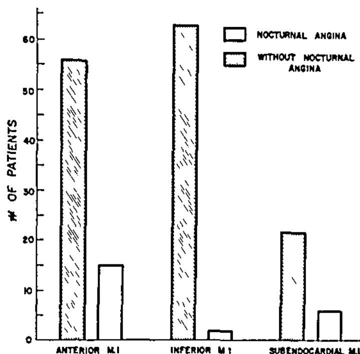


Fig 1 Incidence of nocturnal angina in patients with anterior inferior and subendocardial M I

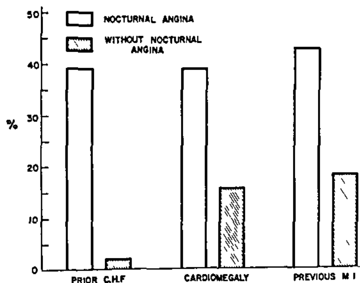


Fig 2 Incidence of prior CHF cardiomegaly and previous MI in those with and without nocturnal angina

Table I MI and nocturnal angina

	No	*Prior CHF*	*Cardio megaly*	*Previous MI*
Patients with nocturnal angina				
Anterior MI	15	4	9	4
Inferior MI	2	0	0	0
Subendocardial MI	6	5	0	6
Patients without nocturnal angina				
Anterior MI	56	2	11	10
Inferior MI	63	1	9	9
Subendocardial MI	22	0	2	6

9/23 patients with nocturnal angina and 22/141 without ($p < 0.02$) Previous myocardial infarction as determined both clinically and electrocardiographically was seen in 10/23 patients with nocturnal angina (43 per cent) and 25/141 (18 per cent) of those without

The significant characteristics of those with and without nocturnal angina are listed in Table I and are shown graphically in Fig 2

Discussion

The three possible mechanisms of nocturnal angina listed by Gorlin[1] include (1) a sympathetic discharge related to dreaming (2) a decrease in blood pressure at night leading to inadequate perfusion of the myocardium and (3) early congestive heart failure

Nowlin and associates and others[3, 4] described the association of nocturnal angina with dreaming These studies monitored rapid eye movements (REM) during sleep to identify periods of dreaming During these REM periods tachycardia and then ST segment depressions were noted, suggesting that the dreaming process was the initiating cause ST segment elevation was noted during REM sleep in one patient with variant angina[6] Although most of the episodes of nocturnal angina and ST segment changes were associated with REM periods occasional episodes were seen during the stage of deep (Stage 4) sleep Possible explanations of the association of nocturnal angina and dreaming include a state of physiologic arousal' which leads to an increase in systolic blood pressure heart rate and respiratory rate and a general sympathetic discharge causing alterations in the coronary circulation[4] Nowlin and associates[3] also suggested that an increased respiratory rate seen shortly after the onset of REM activity could lower arterial carbon dioxide partial pressure, which could lead to decreased coronary artery diameter The association with dreaming could not be determined in our study since we felt that information gathered at the time of admission would not be valid

The autonomic nervous system shows a redistribution of activity during quiet sleep with a general enhancement of parasympathetic over sympathetic activity[7] Blood pressure falls largely due to diminished peripheral resistance and heart rate decreases The possibility that nocturnal angina occurring during periods of quiet sleep

Experimental and laboratory reports

Limitations of the Lown grading system for the study of human ventricular arrhythmias

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In 1971 Lown and Wolf[1] presented a system to grade ventricular arrhythmias in the hospital phase of acute myocardial infarction The grading system has evolved and has been used for classifying ventricular arrhythmias in chronic ischemic heart disease The original grading system or its derivatives has become popular for tabulating ventricular arrhythmias in chronic ischemic heart disease[2-4] Table I shows the grades of ventricular arrhythmias in the currently popular version of the Lown system note that Grades 0 1 and 2 are based on frequency while Grades 3 4A 4B and 5 are based on other characteristics of the arrhythmias It is the purpose of this report to point out certain important shortcomings of the Lown grading system for studying the prevalence of the different ventricular arrhythmias and their relationship to myocardial ischemia myocardial hypertrophy ventricular performance and outcomes—e g sudden death

To illustrate the problems of using the Lown grading system we used it to classify the ventricular arrhythmias in the late hospital phase of acute myocardial infarction in 100 consecutive patients with acute myocardial infarction who lived two weeks and consented to be studied[5] The average age of this group was 61 years (range 25 to 90 years) 71 were male and 29 were female At 14 ± 2 0 days following acute infarction we recorded and analyzed 22 0 ± 1 0 consecutive hours of ECG in each patient (range 18 to 25 hours)

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The ventricular arrhythmias for these 100 patients are analyzed with reference to the Lown grading system in Fig 1 Each of the 100 patients is eligible for Grades 0 1 or 2 on the basis of VPD frequency However characteristics of the ventricular arrhythmias other than frequency made the majority of patients in Grades 1 and 2 eligible for higher grades Thus 64 of 88 (73 per cent) patients with VPDs had multiconfigurational VPDs (Grade 3) 38 (43 per cent) had pairs of VPDs (two consecutive) (Grade 4A) 14 (16 per cent) had ventricular tachycardia (Grade 4B) and 33 (38 per cent) had R on T (Grade 5) The third row of Fig 1 shows the final Lown grade for these 100 patients Note that the actual number of patients who have a peak hourly VPD count either greater than 0 but no more than 30 VPDs (58 patients) or more than 30 VPDs in any hour (30 patients) is not reflected by the number of patients in Grades 1 and 2 This is because 45 of the 58 patients (78 per cent) eligible for Grade 1 and 30 of the 30 patients (100 per cent) eligible for Grade 2 on the basis of VPD frequency also have VPDs with characteristics which qualify them for higher grades and they are finally counted in the highest grade for which they qualify Thus 75 of 88 patients (85 per cent) eligible for Grades 1 or 2 by VPD frequency moved to higher grades Neither does the number of patients in Grades 3 4A and 4B reflect the number who had the VPD characteristics which make them eligible for these grades 44 of 64 patients (67 per cent) with multiconfigurational VPDs 22 of 37 patients (59 per cent) with pairs of VPDs and seven of 14 patients (50 per cent) with ventricular tachycardia moved to higher grades

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2 Nowlin J B Troyer W G Collins W S Silverman G Nicholas C R McIntosh H D Estes E H Jr and Bogdonoff M D The association of nocturnal angina pectoris with dreaming Ann Intern Med 63 1040 1965
3 Editorial Nocturnal angina Lancet 1 732 1972
4 Sleight P Nocturnal angina Letter to the Editor Lancet 1 903 1972
5 Hurst J W The heart ed 3 New York 1974 McGraw Hill Book Company Inc p 1021
6 King M J Zir L M Kaltman A J and Fox A C Variant angina associated with angiographically demonstrated coronary artery spasm and REM sleep Am J Med Sci 265 419 1973
7 Bristow J D, Honour A J Pickering T G and Sleight P Cardiovascular and respiratory changes during sleep in normal and hypertensive subjects Cardiovasc Res 3 476 1969
8 Norris R M Brandt P W T Caughey D E Lee A J and Scott P J A new coronary prognostic index Lancet 1 274 1969
9 Russell R O Jr Hunt D and Rackley C E Left ventricular hemodynamics in anterior and inferior myocardial infarction Am J Cardiol 32 8 1973
10 Williams R A Cohn P F Vokona P S Young E Herman M V and Gorlin R Electrocardiographic arteriographic and ventriculographic correlations in transmural myocardial infarction Am J Cardiol 31 595 1973
11 Hamby R I Hoffman I Hilenrath J Aintablian A Shanes S and Padmanabhan V Clinical hemodynamic and angiographic aspects of inferior and anterior myocardial infarctions in patients with angina pectoris Am J Cardiol 34 513 1974
12 Sharma B Majid P A Meeran M K Whitaker W and Taylor S H Clinical electrocardiographic and haemodynamic effects of digitalis (ouabain) in angina pectoris Br Heart J 34 631 1972
13 Besterman E Nocturnal angina Letter to the Editor Lancet 1 1067 1972
14 Crawford M H LeWinter M M O Rourke R A Karliner J S and Ross J Jr Combined propranolol and digoxin therapy in angina pectoris Ann Intern Med 83 449 1975

A third criticism of the Lown grading system may be raised Since patients are moved to the highest grade attained by the characteristics of their ventricular arrhythmia there is an implication that higher grades carry higher risks of subsequent adverse outcome—e g sudden death If this is so then it could be argued that the Lown grading system is a reasonable one However it has not yet been proven that higher grades carry higher risk In particular there is no evidence that R on T is a more powerful risk factor for subsequent sudden death than ventricular tachycardia and yet seven of 14 patients with ventricular tachycardia were moved to Grade 5 because of the occurrence of R on T In the present state of our knowledge it seems more reasonable to assess the risk of the various VPD characteristics separately and then combine these variables and frequency with other characteristics of ischemic heart disease patients in the search for a combination which best identifies those at highest risk to subsequent sudden death Although multiple configurations pairs of VPDs ventricular tachycardia and R on T are more common in patients with frequent VPDs they also occur in patients with a low frequency of VPDs Using the Lown grading system analysis of a individual characteristic of VPDs such as multiple configurations or R on T cannot be evaluated in published reports separately from frequency for outcomes of interest In our group of 100 patients multiple configurations were seen in 64 patients of these 37 (58 per cent) had a peak hourly VPD count less than 30 and 27 (42 per cent) had 30 or more in at least one hour Further 33 patients had R on T (R V/QT $\leq$ 1 0) of these 17 (52 per cent) had a peak hourly VPD count less than 30 and 16 (48 per cent) had 30 or more The potential problem inherent in using the peak hourly VPD count rather than the average VPD per hour over the entire recording period had been discussed above

Thus the Lown grading system has severe limitations in either cross section or longitudinal studies of ischemic heart disease patients Studies which report their findings using the Lown grading system do not reveal the prevalence of high and low VPD frequency or of the characteristics of Grades 3 4A or 4B Also in examining individual patients the Lown grading system as it is commonly used does not allow one to determine how many different characteristics are present Until more is known about the risk posed by frequency and other characteristics of VPDs we think that each of these should be tabulated separately Lown has recently suggested hourly listing of arrhythmia grade for reporting the analysis of 24 hour ambulatory ECG recordings[6] but this variant of the grading system still poses difficulty in reporting results in groups of patients

REFERENCES

1 Lown B and Wolf M Approaches to sudden death from coronary disease Circulation 44 130 1971
2 Kotler M N Tabatznik B, Mower M M, and Tominaga S Prognostic significance of ventricular ectopic beats with respect to sudden death in the late post infarction period Circulation 47 959 1973
3 Ryan M Lown B and Horn H Comparison of ventricular ectopic activity during 24 hour monitoring and exercise testing in patients with coronary heart disease N Engl J Med. 292 224 1975
4 Schulze R A, Rouleau J Rigo P, Bowers S Strauss H W and Pitt B Ventricular arrhythmias in the late hospital phase of acute myocardial infarction Relation to left ventricular function detected by gated blood pool scanning Circulation 52 1006 1975
5 Wenger T L, Bigger J T, Jr, and Merrill, G S Ventricular arrhythmias in the late hospital phase of acute myocardial infarction Circulation 52 II 110 1975
6 Lown B Calvert, A F Armington R, and Ryan M Monitoring for serious arrhythmias and high risk of sudden death, Circulation 52 III 189 1975

THE KINETICS OF PATIENTS IN THE LOWN GRADING SYSTEM 100 PATIENTS IN THE LATE HOSPITAL PHASE OF ACUTE MYOCARDIAL INFARCTION

	LOWN GRADE						
	0	1	2	3	4A	4B	5
NUMBER OF PATIENTS ELIGIBLE FOR THIS GRADE	12	58	30	64	38	14	33
NUMBER OF PATIENTS MOVING TO A HIGHER GRADE	0	45	30	45	22	7	0
NUMBER OF PATIENTS FINALLY IN THIS GRADE	12	13	0	19	16	7	33

MOVEMENT OF INDIVIDUAL PATIENTS IN THE LOWN GRADING SYSTEM

Fig 1 The movement of patients through the Lown grading system 100 consecutive patients with acute myocardial infarction classified during the late hospital phase of infarction

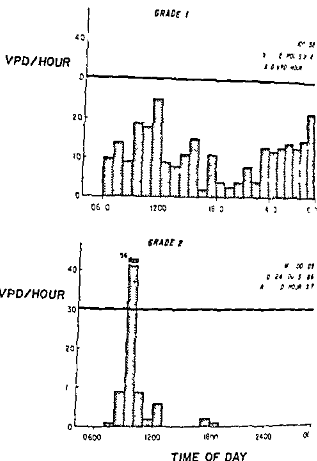


Fig 2 The peak hourly count method of grading frequency of ventricular premature depolarizations (*VPDs*) Frequency histograms of hourly VPD count over a 24 hour period in two patients *Upper panel* patient MI 100-52 is classified Grade 1 even though his average VPD rate was 11 4 because his VPD count did not exceed 30 in an individual hour *Lower panel* patient MI 100 09 is classified Grade 2 because of an hourly count of 56 VPDs between 9 00 A M and 10 00 A M his average VPD rate over 24 hours was 3 7 per hour

Table I The Lown grading system for ventricular arrhythmias

Grade	*Criteria*
0	No VPDs during the monitoring period
1	Peak hourly VPD count 30 or less
2	Peak hourly VPD count more than 30
3	VPDs with more than one configuration
4A	Two consecutive VPDs (pair couplet)
4B	Three or more VPDs (ventricular tachycardia)
5	R on T (R V/QT less than 1 0)

VPDs = ventricular premature depolarizations

Another problem with tabulating frequency of VPDs in the Lown grading system is that patients are allocated to Grade 1 or 2 on the basis of peak hourly counts and the criterion value of 30 This means that, theoretically patients allocated to Grade 1 may have higher average VPD frequency than those allocated to Grade 2 For example a patient with only 30 VPDs per 24 hours (average VPD/hour = 1 3) may qualify for Grade 2 if all his VPDs occur in a single hour Conversely a patient with 696 VPDs per 24 hours (average VPD/hour = 29 0) could be placed in Grade 1 if he had 29 VPDs in each hour of the day The two frequency histograms of Fig 2 illustrate this point Patient No 09 is classified in Grade 2 although he has a 24 hour average of 3 7 VPDs per hour while patient No 52 is classified Grade 1 with a 24 hour average of 11 4 VPDs per hour Admittedly these are the most extreme examples in our sample and are selected to support the present argument In our population there is a very high correlation (r = 0 96) between the peak hourly VPD count and the average number of VPDs per hour calculated by dividing the total number of VPDs in the recording by the number of hours recorded Nevertheless the average VPD per hour and the standard deviation around the average gives better representation not only of the days average but also of the variance in VPDs from hour to hour

vented simultaneous conversion of more than three analog inputs. The three analog inputs to the analog to digital converter, therefore, were unfiltered tape data, tape data filtered through 150 Hz filter, and tape data filtered through 100 Hz filter. The tape was then reproduced a second time with 75 and 50 Hz filters for Channels 2 and 3 and the unfiltered data as previously for Channel 1. The experiment was set up in this way to eliminate obscuring of filtering effects by noise variations which usually occur when taped data are reproduced at different times.

Each record was sampled at 2 msec intervals per channel for 10 sec with a precision of 12 bits (one part in 4,096). A large number of amplitude measurements were made for each cardiac cycle, but only peak Q, R, and S amplitudes are presented here since they describe the observed effects adequately. Effects of filtering are expressed relative to the measurements of the unfiltered ECG, i.e., data sampled from Channel 1. Measurements were computed in two ways: (1) A single cardiac complex from the 10 sec of digitized data for each record was used for all measurements for unfiltered and filtered data. (2) Measurements from each cardiac beat were averaged for the number of beats in 10 sec. Averaged values of filtered data were compared with averaged values of unfiltered data.

No essential differences were noted for results determined in these two ways. The results presented throughout this report, therefore, represent measurements from a single cardiac cycle.

Results

As noted in the Methods section, measurements obtained from unfiltered waveforms were used as the standard for each record. All waveforms in which Q waves were observed for the unfiltered data were put in one group which numbered 70 records. A second group numbering 108 records contained all records in which R waves were observed for the unfiltered data. A third group numbering 75 records was composed of waveforms for which S waves were observed in the unfiltered data. Mean values and standard deviations were then computed for each group for the unfiltered data and for the four different filtered waveforms. To test for significance of differences when subjected to the various filters, the t test for related measures was used.

Table I. The p values of significant differences in Q, R, and S peak amplitudes between unfiltered and various filtered ECG waveforms*

Measurement	150 Hz	100 Hz	75 Hz	50 Hz
Q	–	–	<0.05	<0.02
R	–	<0.001	<0.001	<0.001
S	–	–	<0.001	<0.001

*Statistical test used was t test for related measures.

Significant differences caused by the various filters are shown in Table I. Both the 75 Hz and 50 Hz low pass filters caused significant differences in Q, R, and S amplitudes. The 100 Hz filter caused significant R wave differences only, and the 150 Hz filter had no significant effects on Q, R, or S amplitudes.

To determine the magnitude of differences between filtered and unfiltered amplitudes, a count was made of the number of records in which errors of 10 or 20 per cent were observed. These figures, presented as percentages of records, are shown in Table II. In preparing this table, an arbitrary level of 100 μV was chosen for the difference in amplitude between a filtered and unfiltered measurement. Any record with a difference below this value was judged to be unaffected by the filter, regardless of its percentage error.

When only magnitude of error is considered, regardless of the percentage error, the effects of filtering are shown in Table III. The 50 and 100 μV levels were selected as criteria because those values are close to the precision level normally obtainable by ECG's interpreters from paper recordings.

In most cases when a measurement difference was found between unfiltered and filtered data, only one of the three waves was involved. Only occasionally were both Q and R or R and S reduced significantly for the same record. Therefore, to obtain the percentage of records for which an error in Q, R, or S occurs, the figures in any column in Table II may be added. For a 75 Hz bandwidth, for example, an error in any amplitude greater than 10 per cent may be expected about 6 per cent of the time.

Discussion

The results for 100 Hz bandwidth records obtained from this study of infant ECG's do not differ substantially from those found for adult

Distortions in infant electrocardiograms caused by inadequate high-frequency response

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Reproduction of electrocardiographic (ECG) signals requires certain minimum frequency characteristics for the reproducing system to keep signal distortion below acceptable levels Several reports regarding such distortions have been published in recent years [1-4] The consensus appears to be that adequate representation of the ECG can be obtained with instruments having good frequency response up to 100 Hz In fact the American Heart Association recommendations specify 100 Hz as the minimum bandwidth for routine ECG recording [5] It should be noted that this applies to conventional measurements of P Q R, S and T waves For those investigators interested in low amplitude notches and slurs frequently observed during QRS bandwidths up to 500 Hz may be required for good fidelity of reproduction [6-9]

The published reports dealing with high frequency content have been based largely upon data derived from adult ECG s which normally have QRS durations in the neighborhood of 80 to 100 msec The QRS is responsible for the higher frequencies in the total ECG spectrum The fundamental frequency of a QRS waveform is usually about 10 or 15 Hz with higher harmonics decreasing in amplitude until they virtually disappear at about 100 Hz There has been speculation that ECG's of infants and children may have significantly different frequency spectra because of shorter QRS durations—typically half of those for adult ECG s If so instrumentation requirements might be more stringent in terms of bandwidth for recording and reproduction of ECG s of infants and children than the 100 Hz deemed adequate for adult ECG's The purpose of this report is to present data regarding bandwidth requirements for infant ECG s

Methods

Frank lead ECG s from over 600 infants at the White Memorial Medical Center Los Angeles Calif, were recorded onto frequency modulated tape with the total system bandwidth approximately 0 05 to 600 Hz Individual x, y, and z leads were selected randomly reproduced from tape and subjected to treatment by different low pass analog filters and various amplitude measurements were obtained with a digital computer For 108 leads (47 x leads, 21 y leads and 40 z leads) 50 75 100 and 150 Hz filters were used with the tape data being reproduced twice Each of the four analog filters was constructed with operational amplifiers and resistance capacitance networks such that the transfer function was that of unity gain from zero frequency up to the start of roll off, 3 dB attenuation (voltage gain of 0 707) at the corner frequency (150 100 75 or 50 Hz) and a roll off rate of 12 dB per octave Conventional second order filters with *no resonant peaks* were used

The filters were interposed between tape outputs and analog to digital converter before computer processing Hardware limitations pre

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Table IV Percentage of records in which the difference between unfiltered and filtered amplitudes exceeds 100 μV*

Measurement	100 Hz filter bandwidth		80 Hz filter bandwidth	75 Hz filter bandwidth	50 Hz filter bandwidth	
	Adults	Infants	Adults	Infants	Adults	Infants
Q	0	2	0	2	0	12
R	2	2	7	3	14	16
S	0	0	0	6	4	17

*Data from adults obtained from Table III of Berson and Pipberger

noted in some studies [2, 3] machines in routine use frequently had recording bandwidths well below 50 Hz The 1967 report of the American Heart Association may have had an effect upon this situation Present day machines are available from major manufacturers with bandwidths up to 100 Hz and some more expensive ECG s have bandwidths considerably above this However it is not certain that conditions have improved substantially in the field Recording bandwidth is still often in the neighborhood of 40 or 50 Hz because of either deteriorating performance with age or intentional lowering of bandwidth using switches provided by the manufacturer

In terms of significance there seems to be no question of the effects of filtering on the various waveforms As noted in Table I these effects were observed with very high statistical probabilities even including R wave decreases with 100 Hz bandwidth On the other hand the magnitude of errors occurring at 100 Hz was not judged to be of great importance in that a decrease of greater than 100 μV was observed in only 1 per cent of the records

One interesting by product of this study was the observation that effects of bandwidth limiting were noted even when averaging measurements over several cardiac cycles In most cases averaged measurements were obtained from at least 10 cycles over a 10 sec period and as stated earlier amplitude decreases caused by the filters were seen to about the same extent as for measurements taken from a single cardiac cycle This is another indication that distortion of the ECG waveform by the filters was consistent

Conclusions

Infant ECG signals require a minimum bandwidth of 100 Hz for reproduction to avoid amplitude errors of 10 per cent or greater Although the average infant ECG spectrum is likely to have higher frequencies than the average adult ECG spectrum duration values for Q R and S waves overlap in these populations to such an extent that bandwidth requirements are practically identical

Table V Comparison of mean values and ranges for several measurements for adult and infant ECG s

Measurement	Adults		Infants	
	Mean	96 percentile range	Mean	96 percentile range
QRS duration (ms.)	93	76 – 112	57	40 – [illegible]
R (mV)	1 17	0 51 – 1 97	0 42	0 11 – 0 93
R duration (ms.)	51	29 – 88	23	12 – 36
R (mV)	1 03	0 35 – 1 95	0 76	0 09 – 1 60
R duration (ms.)	61	28 – 100	28	12 – 56
R (mV)	0 93	0 36 – 1 79	1 06	0 40 – 1 75
R duration (ms.)	59	[illegible] – 80	29	20 – 44
Q (mV)	0 41	0 09 – 0 93	1 08	0 53 – 1 9[illegible]
Q duration (ms)	33	20 – 48	23	16 – 36

Summary

Frank lead ECG s from infants were studied for frequency content by introducing low pass filters of 50 75 100 and 150 Hz bandwidths before obtaining computer measurements Results indicated that a minimum bandwidth of 100 Hz is required to avoid amplitude errors of 10 per cent or greater This bandwidth requirement is essentially the same as that required for adult ECG s despite the fact that infant QRS durations are usually about one half those of adults Although

Table II Percentage of records in which errors in amplitude occurred as a result of filtering*

Measurement (of peak amplitude)	150 Hz Filter		100 Hz Filter		75 Hz filter		50 Hz filter	
	Error > 10%	Error > 20%	Error > 10%	Error > 20%	Error > 10%	Error > 20%	Error > 10%	Error > 20%
Q	—	—	—	—	—	—	4	1
R	1	1	1	1	3	1	10	4
S	—	—	—	—	3	—	11	5

*Error is defined as the difference in amplitude between the wide band and the filtered waveform (same cardiac cycle) divided by the unfiltered measurement value Errors in amplitude between unfiltered and filtered records less than 100 μV are considered as no errors

Table III Percentage of records in which the difference between unfiltered and filtered amplitudes exceeds 100 or 50 μV*

Measurement	150 Hz filter		100 Hz filter		75 Hz filter		50 Hz filter	
	$\epsilon > 100\ \mu V$	$\epsilon > 50\ \mu V$	$\epsilon > 100\ \mu V$	$\epsilon > 50\ \mu V$	$\epsilon > 100\ \mu V$	$\epsilon > 50\ \mu V$	$\epsilon > 100\ \mu V$	$\epsilon > 50\ \mu V$
Q	0	10	2	13	2	13	12	30
R	1	8	2	10	3	28	16	53
S	0	5	0	11	6	22	17	43

*For each measurement the total number of records is different depending upon the presence of that wave in the unfiltered record

ECG s For example, in a group of adult records Berson and Pipberger[3] reported R wave reductions of over 0 10 mV in 2 per cent of their records using a 12 dB/octave low pass filter No such differences were found for Q and S waves These results compare with 2 per cent of the records for Q and R waves from infants in this study with a 100 Hz bandwidth filter Table IV lists comparisons between the two studies for Q R, and S amplitudes for bandwidths between 50 and 100 Hz Considerable differences in the kinds of errors between adult and infant records occur at 50 Hz bandwidth and fewer differences occur at 75 and 80 Hz The energy spectra of both adult and infant ECG s appear however to drop rapidly in a similar manner in the neighborhood of 100 Hz

For adult ECG s Berson and Pipberger[3] studied the effects of filter roll off characteristics using 6 12 and 24 dB/octave filters Their results indicated that amplitude errors were not directly related to the roll off rate for the same nominal cutoff frequencies In the present study, only a single roll off rate (12 dB/octave) was used since most direct writing electrocardiographs behave as either second order or third order low pass systems

Apart from low amplitude notches and slurs the high frequency content in an ECG waveform results from the QRS configuration Draper and co workers[11] published data of mean values and ranges for adult males, a partial listing is shown in Table V Also in this table are similar data obtained from 666 infant ECG s in which ages ranged from 1 to 72 hours[1] Although amplitude values for some measurements are greater for adults than for infants the reverse is true for others Durations, on the other hand are consistently lower for infants than for adults

It is well known that an inverse relationship exists between pulse width and bandwidth for periodic pulses Since the QRS in an ECG signal may be considered as a periodic pulse a higher bandwidth would appear to be necessary for reproducing the smaller duration infant QRS waves On the average, this is probably true However the large ranges in durations observed for adults account for the need for comparable bandwidths for infant and adult records For example the lower range of duration for Q waves in Lead z is practically the same in both instances (Table V) The data in Table IV can also be interpreted in this light by noting that although errors were found for both infants and adults with bandwidths up to 100 Hz infant ECG records were more sensitive to errors for bandwidths greater than 50 Hz

Until several years ago, most commercially available ECG machines were not capable of recording with bandwidths up to 100 Hz and, as

Pathology of sinoatrial node Correlations with electrocardiographic findings in 111 patients

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The responsibility of histological disorders of the sinoatrial node (SAN) in abnormal atrial rhythms has not yet been clearly defined In order to establish such correlations the SAN of 111 patients was studied by serial sections The electrocardiographic findings in this series include patients with sinus rhythm patients with atrial flutter or fibrillation and patients presenting various arrhythmias

Materials and methods

The pathology of the SAN was studied in 111 patients Only those patients in whom sufficient clinical data and electrocardiographic findings for a period of four weeks or more were available were included in this group

Every case had a gross examination of the heart Dissection of the three main coronary arteries and their collateral branches of 1 mm or more in diameter was performed. The cavo auricular junction was removed Each specimen contained the superior vena cava up to the point of pericardial reflection the crest of the right atrial appendage and the upper third of the right atrium The part was fixed in a 10 per cent formalin solution paraffin embedded and sliced into 8 μ thick serial sections One section out of ten was stained (Masson s trichrome) The sinus node artery examined in the part included in the block was about three centimeters long Its initial part rising from the main coronary artery was therefore not examined The per cent of nodal cells in relation to fibrous elastic or fatty tissue was determined by visual count the slides were projected (Mikro Promar Leitz) on to a screen and cross checked with 10 vertical and 10 horizontal lines to produce 100 intersections each of which was observed and noted to its similarity either to a nodal fiber or collagen Twenty slides equally distributed in each sinus node were analyzed according to this procedure (Fig 1)

In twenty cases the inter atrioventricular septum was removed and divided into a rectangular block limited on the upper edge by the fossa ovalis inferior part following the atrioventricular rings at the lower edge by the septal insertion point of papillary muscle of the tricuspid valve behind by the coronary sinus ostium and forward by the anterior edge of the moderator band This block was sliced into serial sections in order to study the AV system and the His bundle and its branches One section out of ten was stained and studied

Results

The results were classified according to the ECG analysis

1 Subjects in sinus rhythms The percentage of nodal cells in 26 subjects under 60 years of age and in 36 subjects over 60 years of age were studied The results are summarized in Fig 2 There was a higher amount of fibrosis in the older group as compared with younger group This difference is statistically significant ($P < 0\,001$)

2 Atrial fibrillation and atrial flutter The

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the average infant ECG spectrum is likely to contain higher frequencies than the average adult ECG spectrum, duration values for Q R, and S waves overlap in these populations to such an extent that bandwidth requirements are practically identical

REFERENCES

1 Scher A M and Young A C Frequency analysis of the electrocardiogram Circ Res 8 344 1960
2 Dower G E Moore A D Ziegler W G and Osborne J A On QRS amplitude and other errors produced by direct writing electrocardiographs Am Heart J 65 307 1963
3 Berson A S and Pipberger H V Electrocardiographic distortions caused by inadequate high frequency response of direct writing electrocardiographs Am Heart J 74 208 1967
4 Golden D P Jr Wolthuis R A and Hoffler G W A spectral analysis of the normal resting electrocardiogram IEEE Trans Biomed Eng 20 366 1973
5 Pipberger H V et al Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography Report of the Committee on Electrocardiography American Heart Association Circulation 52 (August issue) 11 1975
6 Langner P H Jr The value of high fidelity electrocardiography using the cathode ray oscillograph and an expanded time scale Circulation 5 249 1952
7 Geselowitz D B Langner P H Jr and Mansure F T Further studies on the first derivative of the electrocardiogram including instruments available for clinical use Am Heart J 64 805 1962
8 Flowers N C Horan L G Tolleson W J and Thomas J R Localization of the site of myocardial scarring in man by high frequency components Circulation 40 927 1969
9 Flowers N C and Horan L G Diagnostic import of QRS notching in high frequency electrocardiograms of living subjects with heart disease Circulation 44 60[illegible] 1971
10 Bruning J L and Kintz B L Computational Handbook of statistics Glenview Ill 1968 Scott Foresman and Company p 12
11 Draper H W Peffer C J Stallmann F W Littmann D and Pipberger H V The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system) Circulation 30 853 1964
12 Guller B Lau F Y K Dunn R A Pipberger H A and Pipberger H V Computer analysis of changes in Frank vectorcardiograms of 666 normal infants in the first 72 hours of life Am Heart J (submitted for publication)
13 Kossmann C E et al Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography Report of Committee on Electrocardiography American Heart Association Circulation 35 583 1967

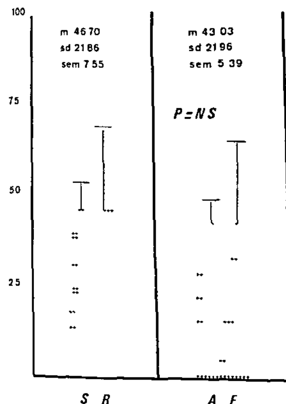


Fig 3 Comparison within an age group of the per cent amount of nodal cells (per cent represented on the y axis) between a group of patients with sinus rhythm and a group of patients with atrial fibrillation SR = sinus rhythm AF = atrial fibrillation. P is not significant

6 Chaotic atrial rhythm (one case) (Defined according to Kones and associates[1] as the presence of P waves of different morphologies—three kinds at least—absence of any prevailing atrial focus variations in PR PP and RR intervals and an isoelectric PR segment) In this case the SAN was normal However there were myocarditis lesions in the atrium and infiltration of the peri sinusal nerve ganglia by inflammatory cells

Discussion

Criticism of the method Even if all the patients were surveyed with ECG recorders at least one month before death some of them were not submitted to extended continuous monitoring in a few cases several kinds of atrial arrhythmias listed may have occurred sporadically in the same patient and without continued monitoring over very long periods of time may also be suspected to have occurred even in the patients we classify in the sinus rhythm group



Fig 4 Sinus node of a 7? year-old man undergoing a chronic sinoatrial block In the right inferior corner is the sinoatrial node artery *(sna)* The SAN appeared a fibrotic block In this node the amount of nodal cells was lower than 5 per cent (Masson s Trichrome stain)

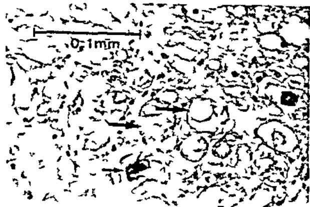


Fig 5 Lesions of the atrial muscle in auricular bradycardia-tachycardia syndrome Atrial fibers seems ballooned *(thin arrows)* with nuclei lesions *(thick arrows)* (Masson s Trichrome stain)

Furthermore it is well known that many atrial arrhythmias are transient and we may or may not have received a true picture with brief periods of ECG examination But in spite of this criticism we think that in most cases monitoring and ECG data were sufficient to reflect an accurate picture on various arrhythmias

Percentage of nodal cells and age In 1954 Lev observed that sclerosis increased with age This was discussed by Hudson in 1965[3] Studies by Davies and Pomerance and by Sims[5] have shown that there was an increase in fibrosis as subjects grew older Our results support the concept of SAN senescence phenomenon However two points must be noted in this respect (a) some sinus nodes are not only fibrous but also atrophic

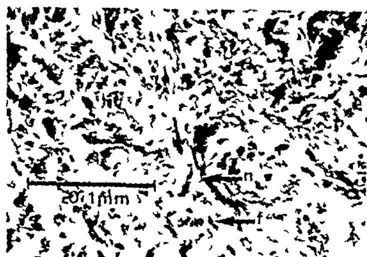


Fig 1 Normal sinus node (17 year-old girl) The slide is projected on a screen with a 100 point grid display Points coincide with either nodal fibers *(n)* or fibrotic tissue *(f)* Thus it is possible to calculate the per cent amount of nodal cells in relation to fibrotic tissue (Masson s Trichrome stain)

amount of nodal cells in 58 patients with sinus rhythm was compared with the amount of nodal cells in 29 patients with atrial fibrillation or atrial flutter in one age group (> 40 years old) The results are summarized in Fig 3 The percentage of nodal cells was slightly lower in the group of patients with atrial fibrillation but the difference between these two groups was not significant

3 Sinoatrial blocks (Defined as sinus pauses with or without junctional escape, or as the absence of atrial activity on the electrocardiogram, while it was still possible to pace the right atrium electrically) This group includes 12 patients Eight subjects showed chronic sinoatrial blocks and four had sinoatrial blocks of recent appearance (less than 15 days before death) In the chronic sinoatrial block group, the SAN appeared as a fibrotic block the amount of nodal cells was lower than 5 per cent (Fig 4) In two cases however this amount was between 15 and 20 per cent Three patients furthermore had occurrences of AV block Mobitz type 1 with narrow QRS during the evolution The histological examination of these three patients revealed severe fibrosis near the AV node and, in one case, of the AV node itself The bundle of His and its branches showed only slight fibrosis The SAN of the four patients who had recent appearance of sinoatrial blocks showed less severe lesions (40 per cent ± 10) In three cases metabolic alterations may have been responsible infarction of the atrium and sinus node adjacent tissue was present in one case

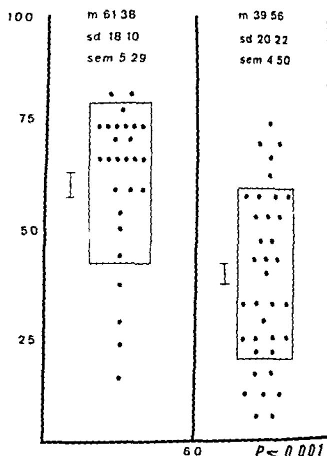


Fig 2 Comparison between the per cent amount of nodal cells in subjects under 60 years of age *(left)* and over 60 *(right)* On the y axis percentage of nodal cells *m* = mean *sem* = standard error of the mean *sd* = standard deviation $P < 0.001$

4 Auricular bradycardia–tachycardia syndrome (Defined as the alternance of symptomatic sinus bradycardia and episodes of atrial tachyarrhythmias namely atrial fibrillation or flutter) There were six cases in this group In five cases, considerable nodal cell deficiency was found in the sinus node (< 15 per cent) associated in four cases with lesions of the atrial muscle (hemorrhage fiber degeneration, fibrosis) (Fig 5) Two of these patients demonstrated episodes of AV blocks In one with Friedreich s disease the SAN was found to be normal

5 Permanent atrial standstill (one case) (Characterized by the absence of electrical and mechanical activity of the atrium and lack of response to atrial pacing) The SAN and approaches of the SAN had become a fibrotic block The remainder of the atrium was involved by atrial myocarditis the etiology of which has not been determined Muscular fibers were ballooned, vertical and transverse striation had disappeared, and the nuclei showed very important injuries (picnosis and carryorrhexis) The AV system and the bundle of His were normal

number of histological studies[3, 1, 17, 2] which showed as in the present report the existence of lesions of the SAN associated with lesions of the atrium. It is quite possible to conceive that attacks of supraventricular tachycardia are favored by the sinoatrial node failure which allows atrial escapes Moreover the atrial fibrosis areas offer an ideal pathway for circus movement Both mechanisms may exist separately or together

The same alteration is found in our case of chaotic rhythm and in cases of permanent atrial standstill reported by Ro en and associates [3] and Brechenmacher and colleagues [21] However the SAN appeared normal in architecture but disconnected from the right atrium by fat and scattering of fibrosis in another atrial standstill case recently published by James and Puech [22]

Etiology

In this series the etiology of the organic affection of the SAN was positively established in only a small number of cases infiltration of the SAN during carcinomatosis (Fig 6) or infectious pericarditis (5 cases) infarction of the atrium spreading to the SAN (2 cases) (Fig 7) In the other observations there were varying degrees of fibrosis the etiology of which is not clear The fibrosis may only affect the SAN whose nodal cells degenerate become highly vacuolated poorly stained The nodal cells are progressively replaced by fibrous and elastic tissue [3] In some cases the SAN is so atrophic that it is reduced to a thin sleeve surrounding the artery (often with lipidic infiltration) Fibrosis may affect the SAN only or on the other hand involve the approaches of the AV node and the AV node itself In the majority of cases these lesions do not appear to be of ischemic origin Thus in our series there was no difference between the pathology of the coronary arteries of subjects presenting atrial arrhythmias and of patients in the same age group in sinus rhythm although some part of the sinus node artery had escaped microscopic examination The same observation was made by Engel and colleagues who examined the coronary arteriographies of a group of subjects with sinus rhythms and a group suffering from depressed sinus node function Hudson pointed out that atheromatous lesions of the SAN artery are rare Davies and Pomerance have observed that thrombosis of the SAN artery may leave intact the SAN itself It appeared to us moreover that the right coronary artery which supplies the SAN in 60 per cent of the cases was seldom the site of major lesions before the branching off of the SAN artery However James has reported several observations in which a lesion of the proximal portion of the right coronary artery was responsible for an infarction of the SAN The etiology of this does not appear clearly on histological examination It is likely that advances in the methods of histochemical diagnosis more specifically will contribute to elucidate the etiology of the SAN lesions

Summary

Histological study of the sinoatrial node (SAN) was performed in 111 patients in order to establish correlations between the ECG findings and the anatomical lesions This series includes both patients with sinus rhythm and patients with atrial arrhythmias The results are as follows (a) the amount of nodal cells in the SAN was found to be inversely proportional to the age of the patients ($p < 0.001$) (b) normal sinus rhythm was present in some cases with severe fibrosis of the SAN (c) the present study does not support lesions of the SAN as responsible for atrial fibrillation (d) chronic sinoatrial block was associated with extensive lesions of the SAN occasionally combined with lesions of the approaches of the AV node or of the AV node itself (e) the auricular tachycardia-bradycardia syndrome was associated in most cases with both lesions of the SAN and the atrial muscle (f) fibrosis was the main feature of the SAN lesion The pathogenesis of these fibrotic lesions are discussed

REFERENCES

1 Kones, R J Phillips J H and Hersh J Mechanism and management of chaotic atrial mechanism Cardiology 59 9? 1974

2 Lev M Aging changes in the human sinoatrial node J Gerontol 9 1 1954

3 Hudson R B Cardiovascular pathology London 1965 Edward Arnold Ltd vol. I p 96

4 Davies M J and Pomerance A Quantitative study of ageing changes in the human sinoatrial node and internodal tracts Br Heart J 34 1?0 19?2

5 Sims B A Pathogenesis of atrial arrhythmias Br Heart J 34 336 19?2

6 Rossi, L. and Levy A Atteinte du noeud sinusal et du système neuroganglionnaire a rial par une tumeur primitive maligne du péricarde (mésothéliome) Arch Mal Coeur 54 807 1961

7 Brooks Ch Mc and Hsin Hsiang Lu C The sinoatrial pacemaker of the heart Springfield Illinois 19?2 Charles C Thomas p 1?0

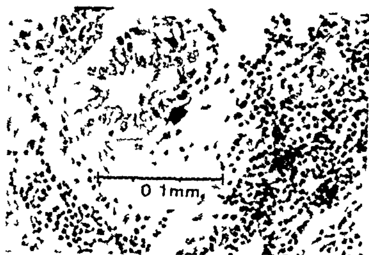


Fig 6 Metastasis of a bronchial carcinoma *(arrow)* in the SAN surrounded with inflammatory cells (Masson s Trichrome stain)



Fig 7 Hemorrhage into the SAN *(arrows)* during infarction of the atrium spreading to the SAN In the right inferior corner is the sino atrial node artery *(sna)* On the left side atrial myocardium (Masson s Trichrome stain)

(b) some patients maintain a sinus rhythm with only 10 per cent of nodal cells It seems that a very small amount of nodal cells is enough to maintain a sinus rhythm [6] It is possible that nodal cells located close to the SAN area are able to take over the pacemaker function when it becomes inadequate [7]

Atrial fibrillation or flutter Controversy exists regarding the responsibility of organic lesions of the SAN in the genesis of atrial flutter or fibrillation Many observations have been reported in the literature[1, 8, 9] in which atrial fibrillation was related to lesions in the SAN According to Davies and Pomerance [10] there is a difference between long term atrial fibrillations and short term fibrillation For these authors the SAN is normal in short term fibrillation whereas there is reduced percentage of fibers in long term fibrillation According to the authors it is possible that the fibrotic changes in the node and atria result from the arrhythmia and consequent disordered function of the chambers Except for this point, our results show that the nodal fibers percentage is similar in the sinus rhythm group and in the atrial fibrillation patient group We have not established any distinction between these two groups, for the following reasons (a) It was difficult in a number of cases to know how old the atrial fibrillation was (b) Some cases of atrial fibrillation are difficult to classify, such as atrial flutters which appear or disappear in the course of an infectious disease or after DC countershock (c) Atrial fibrillation may appear in some patients before death, possibly under the influence of metabolic or anoxic alterations The results of our study show that SAN lesion is not a necessary nor sufficient condition for atrial fibrillation to develop At most this may be a predisposing factor among many others such as distension of the atria lesions of myocarditis or fibrosis or increased vagal tone

Chronic sinoatrial blocks Chronic sinoatrial blocks seem to be related to extensive lesions of the SAN The results of this study corroborate those of the literature [8, 7, 11, 14] These anatomo-pathological facts therefore are more in favor of a temporary failure of the SAN to generate an impulse rather than a failure of this impulse to be conducted from the SAN to the atrium In two patients 15 to 20 per cent of sinus node fibers were still present This percentage of nodal fibers can be observed in sinus rhythm patients Therefore it is obvious that if the optic microscopy is sufficient to give the percentage of collagen and optically normal nodal fibers this method is not suitable to prove that a morphologically normal cell is functionally healthy The association of a chronic sinoatrial block with an AV block is more than coincidental in a previous report[15] of 84 cases of chronic sinoatrial blocks followed over a long period there were 11 patients (13 per cent) also with AV blocks The reason of this association is still obscure The number of histological studies reported is too small[13, 16] to allow a definite opinion It is difficult to know if this combination is the result of the same disease involving both the SAN and the AV node (probably degenerative) or of two different diseases

Auricular bradycardia-tachycardia syndrome This syndrome has been the subject of a limited

Ventricular buckling A factor in the abnormal ventriculogram and peculiar hemodynamics associated with mitral valve prolapse

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Although idiopathic mitral valve prolapse (click-murmur or Barlow s syndrome)is usual ly benign certain patients have significant mani festations implying ventricular involvement These include T wave changes chest pain a distorted ventriculogram ventricular arrhyth mias and very rarely sudden death In 1970 chiefly on the basis of anatomic observations we suggested the following theory Prolapse no matter how it begins may increase stress on the whole mitral apparatus especially the papillary muscles and their sites of insertion significant ventricular manifestations are probably mainly due to papillary muscle involvement Various aspects of this theory have also been presented by other workers Sometimes *in our view* the ventriculogram suggests that one or both papil lary sites buckles--is pulled inward by the valve sail Ventricular arrhythmias might be due directly to papillary stretching which in an ex perimental preparation has been shown to reduce propagation of action potentials and to excite local pacemaker activity [8] Atrial arrhythmias as p oposed by Wit and associates could originate from the abnormally tensed leaflet Theoreti cally all these manifestations might be benefited by mitral valve replacement but practically most patients do not have problems serious enough to warrant such drastic therapy

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Because of this hypothesis we decided to replace the mitral valve in a patient with mild mitral regurgitation and life threatening ar rhythmias hope of preventing death from ventricular fibrillation was the only reason for surgery Thus we were given the opportunity of studying other effects of untethering the papil lary muscles Would T wave changes improve? Would the ventriculogram change? Grossman who first described the systolic invagination considered it a primary contraction ring [10] If this is true the findings in some form should persist even after removal of the mitral valve [2] But if the proposed theory is correct an opposite effect might be expected Pre and postoperative studies have now been done in four cases of severely symptomatic mitral prolapse not due to chordal rupture Peculiar clinical and hemodynamic features were noted in this group A follow up study of eight other patients with similar clinical findings has been made

Case History

A 39 year old woman was first referred in 1971 for evaluation of a murmur T wave changes and ventricular ectopic beats (PVC s) discovered in 1966 during a severe febrile illness Auscultatory findings led to a diagnosis of idiopathic mitral prolapse but associated aortic regurgitation was mistakenly thought to be present because the murmur prominently bridged the second heart sound the apparently diastolic portion being longer than the systolic (see Results section) By palpation the apex impulse was brief but had large excursion All apex cardiograms showed midsystolic collapse with the click at its nadir findings characteri tic of mitral prolapse early

8 Rossi L Histopathology of the conducting system G Ital Cardiol 2 484 1972
9 James T Myocardial infarction and atrial arrhythmias Circulation 24 761 1961
10 Davies M J and Pomerance A Pathology of atrial fibrillation in man Br Heart J 34 520 1972
11 Lippestad C and Marton, P Sinus arrest in proximal right coronary artery occlusion AM HEART J 74 551 1967
12 Rasmusen K Chronic sino atrial block AM HEART J 81 38 1971
13 Rosen K Rahimtoola S Gunnar R and Lev M Transient and persistent atrial standstill with His bundle lesions Electrophysiologic and pathologic correlation Circulation 44 220 1971
14 Davies M J Pathology of conducting tissue of the heart London 1971 Butterworth & Co Ltd p 154
15 Warembourg H Thery C Lekieffre J Delbecque H and Gosselin B Blocs sino auriculaires et blocs auriculo ventriculaires associés Etude anatomo clinique Arch Mal Coeur 67 787 1974
16 Rosen K Rahimtoola S Gunnar R and Lev M Site of heart block defined by His bundle recording Patho logic correlations in three cases Circulation 45 965 1972
17 Rossi L Conducting and nervous system of the heart in atrial arrhythmias A clinico pathological study of 33 cases Acta Cardiol 21 34 1966
18 Acar J Hammou J C Diradourian J C Lellouch A and Delcourt A Troubles du rythme et de la conduc tion et amylose A propos d un cas anatomo clinique Ann Med Interne 121 703 1970
19 Kaplan B M Langendorf R., Lev M., and Pick A Tachycardia-bradycardia syndrome (so called sick sin us syndrome) Am J Cardiol 31 497 1973
20 Kulbertus H E de Leval Rutten F and Demoulin J Sinoatrial disease a report on 13 cases J Electrocardiol 6 303 1973
21 Brechenmacher C Coumel P and Slama R Paralysie auriculaire apparente et troubles de la conduction auric ulo ventriculaire Etude anatomo clinique Arch. Mal. Coeur 68 575 1975
22 James T and Puech P De Subitaneis Mortibus IX Type A Wolff Parkinson White syndrome Circulation 50 1264 1974
23 Balsaver A Morales A, and Whitehouse F Fat infiltration of myocardium as a cause of cardiac conduc tion defect Am J Cardiol 19 261 1967
24 Engel T R Meister S G and Feitosa G S Func tional appraisal of sinus node artery disease Circulation 52 286 1975

diastolic movements could not be recorded By ECG the T waves were sharply inverted in the inferior and lateral leads (Fig 1) Nine previous records showed this to be a constant finding Ectopy was increased by exercise PVCs appeared unifocal showing a pattern of right bundle branch block with an axis of −135°—negative in all leads except aV_R V_1 and V (Fig 1) Vector analysis suggested that they arose from the posterior ventricular wall nearer the apex than the base[11] in an area close to the posterior papillary site Therapy had been difficult quinidine produced fever propranolol did not seem to help and procainamide was of questionable benefit The diagnosis of severe mitral prolapse was confirmed by cardiac catheterization done elsewhere in 1972

The patient was next referred in October 1973 after a prolonged near fatal episode of ventricular fibrillation Upon her transfer to Emory University Hospital temporary evidence of brain damage had cleared Yet continuous monitoring showed frequent runs of ventricular tachycardia despite complete bed rest and propranolol in doses up to 400 mg per day The ventriculogram showed sudden marked late systolic inward movement of the papillary sites and exaggerated ventricular emptying which seemed to parallel a large late systolic secondary phase of mitral prolapse Mitral valve replacement was done after one month of observation With the heart exposed surface mapping of the ventricular ectopic beats localized earliest epicardial breakthrough to an area over the site of the posterior papillary muscle (Fig 2) A medium sized Beall valve was inserted The pump run was brief the operation and convalescence went smoothly Postoperative cardiac size by x ray and coronary arteriogram remained normal The postoperative ventriculograms showed that segmental hypokinesis had appeared in precisely the areas with the greatest movement on the preoperative study The apex impulse became broader and more sustained A follow up apexcardiogram showed that the systolic notch was absent and that diastolic movement now could be easily recorded In the immediate postoperative period the patient developed an increased PR interval and downward sloping ST segments in the absence of digitalis This however progressively improved so that within two months the PR was 0 16 and T waves were almost normal PVCs disappeared almost completely for three months but then reoccurred finally responding to a combination of propranolol and diphenylhydantoin In June 1974 abrupt omission of antiarrhythmic therapy produced no change in the resting electrocardiogram but standing now inverted the T waves and exercise led to ectopic beats and runs of ventricular tachycardia Restoring propranolol alone gave substantial but incomplete protection from orthostatic arrhythmias Now 24 months postoperatively on both medications the patient leads a completely normal life Although we appreciate that rebound effects may occur after abrupt withdrawal of long term propranolol we have made no further attempts to discontinue combined antiarrhythmic therapy At present even the standing and postexercise electrocardiograms are virtually normal

Epicardial Mapping Of Ventricular Ectopic Beats

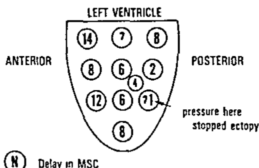


Fig 2 Intraoperative epicardial mapping of the left ventricle (Case I) QRS peaks of ventricular ectopic beats were recorded in 11 different locations and compared with those in Lead II of the simultaneously recorded surface ECG (see text)

Results

An unusually close correlation was possible between preoperative phonocardiograms and angiocardiograms using echocardiography as an intermediary Simultaneously recorded echo and phonocardiograms showed that the first sound (S 1) always virtually coincided with mitral closure (MC) and that the click (C) always occurred at the onset of a second very rapid phase of mitral prolapse (Fig 3) Both these points could be easily identified with cineangiography which was done at a speed of 60 frames per second so that the frame interval of 16 7 msec was close enough to allow useful correlation Control phonocardiograms were done on six separate occa

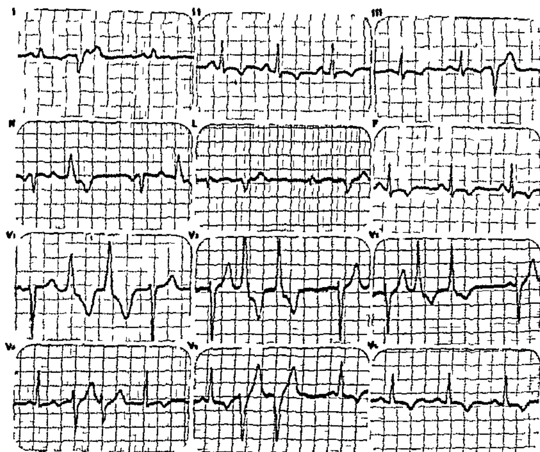


Fig 1A Preoperative electrocardiogram Case I

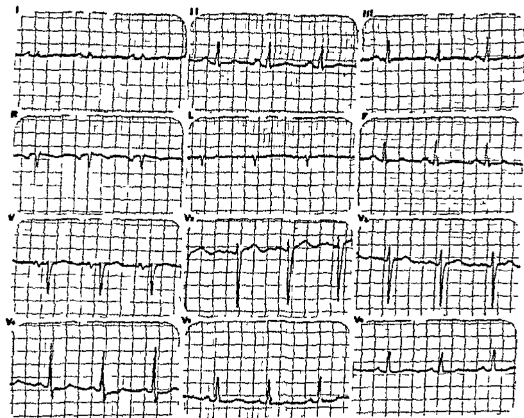


Fig 1B ECG Case I three months postoperatively Both tracings (*Figs 1A* and *1B*) were taken with the patient recumbent and off all medication for 48 hours

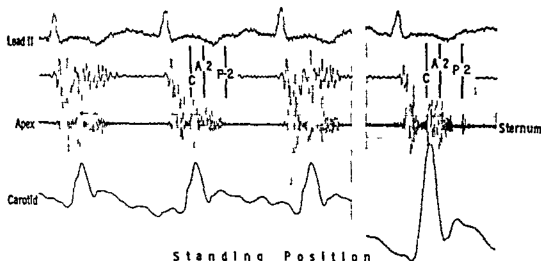


Fig 4 Phonocardiogram (Case I) C = mitral click $A\ 2$ and $P\ 2$ = aortic and pulmonic components of the second heart sound the latter widely separated and not recorded at the apex Paper speed 100 mm per second. Standing widened the C A 2 interval from 35 msec to 60 msec failed to close the split S 2 Murmur continues over 90 msec after the onset of A 2 which occurs on the upstroke of the T wave Postoperatively A 2 fell in its normal position 30 to 40 msec after the end of the T wave

A 2 Beginning with the click it extended 35 msec to aortic closure and then 60 to 70 msec into what would ordinarily have been considered diastole At first this seemed incomprehensible But both the angiogram and echos of the septum showed that the ventricle continued to shrink after A 2 (Figs 5 and 6 *C D E*) Thus it appeared that the murmur was indeed purely systolic but largely post ejection On the angiocardiogram by frame count analysis it could be seen that this *post ejection systole* dumped its blood into an enlarging mitral pouch with much also escaping past the valve free into the left atrium (Figs 5 and 6 *D E*)

4 *A remarkably split second heart sound* The nature of an early diastolic sound averaging 100 msec after A 2 was hardest to define (Figs 3 and 4) Intracardiac phonocardiography was not available An early diastolic sound has been encountered in other cases and appears best explained as the obverse of the systolic click or as an opening snap The following evidence opposed this explanation and suggested that the sound in the present case was the pulmonic component of the second sound (P 2) (a) Correlated angiography and echocardiography demonstrated that the sound occurred while the leaflets were still severely prolapsed in the left atrium (Fig 3) (b) The sound was best heard high along the left sternum and was inaudible at the apex (c) Fixed at 100 msec after A 2 regardless of heart rate or exercise it nonetheless widened by 20 msec with inspiration though it failed to narrow with standing (d) Studied at a variety of heart rates it closely followed the predicted Q P 2 interval based on Weissler s formula[1] and fell just after the T wave of the ECG retaining its relation to the T wave when further separated from A 2 during the extra shortening of ejection time produced by post PVC beats (e) During bigeminal rhythm it had the same appearance and transmission as the widely split P 2 of the right bundle branch block PVC s (f) Fusion beats further widened separation from A 2 (to 140 msec) probably because of the added effect of delayed right ventricular activation

During the first week postoperatively close normal splitting of S 2 was noted and Q A 2 time became normal though PEP was even longer than preoperatively Three months later all systolic time intervals had become normal

Angiocardiogram Studies were made on 35 mm film at 60 frames per second three days after withdrawal of propranolol Recognition of the ventricular sites of papillary muscle insertion was based on our own postmortem studies and the not infrequent visualization of papillary muscles in normal angiograms usually during the augmented emptying occurring after a ventricular ectopic beat Although there is considerable normal variation the papillary sites are fairly predictable the posterior papillary muscle inserts

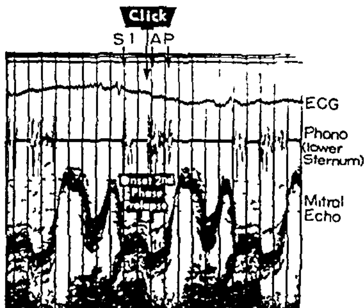


Fig 3 Simultaneously recorded echo and phonocardiograms (*Case I*) *Note that the click* occurs at the onset of a second more rapid phase of prolapse and initiates a murmur bridging the aortic component of the second heart sound (*A*) which is separated by about 100 msec from the pulmonic component (*P*) Time lines 100 msec apart

sions at rates varying from 50 to 120 Three hundred beats were analyzed showing that during recumbency the interval between the click and the aortic component of the second sound C A 2 time) was unusually constant at 35 msec ± 5 msec regardless of heart rate or volume load It was necessary, however to prove that angiography did not change this interval Thus phonocardiograms were also done immediately before and after the studies The C A 2 time remained 35 msec The S 1 C interval increased by 40 msec, on angiography the corresponding measurement, the MC C interval increased by 50 msec (3 frames) This small change probably resulted from acute volume loading and can be seen in the lateral angio view (Fig 6) which was recorded at the second injection The A 2 point on the angiogram was calculated by adding two frames (33 msec) to the click point This calculated A 2 point correlated with actual *aortic valve closure* (visible in the lateral view) by 0 to 1 frame These close correlations allowed plotting of the phonocardiogram and angiogram together (Figs 5 and 6) Angiographic and echocardiographic as well as most phonocardiographic studies were done 48 to 72 hours after withdrawal *of propranolol*

Echocardiogram (Fig 3) Findings were constant during three different examinations The mitral leaflets at the time of closure were already apparently in prolapsed position, i e they both closed posterior to the *aortic ring in a strip chart* recording As systole progressed the initial phase of prolapse continued a slow backward movement just keeping pace with the anterior rotation *of the heart As a result, there was a horizontal* mitral tracing instead of the normal anterior swing Then beginning abruptly with the click there was a much larger very rapid second phase *of prolapse In many different cycles the click* was always the signaling event The onset of the second rapid phase could also be easily identified *angiographically and* was always *paralleled* by the onset of the peculiar invagination of the ventricle postulated to be buckling Both echo and angiograms showed that ventricular ectopic beats failed to produce the click the second phase of prolapse, or ventricular buckling' Thus, the *three events seemed closely interrelated By* echo cardiogram septal motion appeared normal, but good records of the posterior wall were not obtained

Phonocardiogram (Figs 3 and 4) There were four remarkable features

1 *Striking abbreviation of ejection* associated with premature aortic valve closure A 2 which normally falls about 30 msec after the end of the T wave of the ECG was recorded at the peak of the T wave (the Q T interval was normal) A 2 was validated by its relation both to the carotid *pulse and to aortic closure defined* echocardiographically Systolic time intervals were measured and compared with normal values derived from Weissler s regression equation [14] The period from the onset of the Q wave to the onset of A 2 (Q A 2 time) for 300 cardiac cycles was found generally to be 70 to 100 msec less than expected Phonocardiograms taken in *1966 and 1971* showed the same remarkable abnormality The left ventricular ejection time (LVET) was similarly reduced By contrast pre ejection period (PEP) was slightly prolonged Early ventricular ectopic *beats (PVC s with a coupling* interval of less than 60 per cent of the previous RR interval) decreased the Q A 2 time of the next sinus beat even more 130 to 140 msec

2 *The systolic click was unusually close to A 2* at 35 to 45 msec during recumbency scarcely varying at all over a range of heart rates from 50 to 120 Standing widened the interval slightly *to* 60 to 65 msec

3 *The systolic murmur prominently bridged*

Fig 6 Ventriculogram left lateral view (Case I) Captions as in *Fig 5* Heart rate identical in pre and postoperative study The striking preoperative finding was normal ventricular movement before the click point but then very rapid buckling and concomitant acceleration in mitral prolapse At end systole *(E)* note the tiny ventricular cavity the bulging cauliflower shaped valve and the tip of the papillary muscle within the mitral ring Even after the end of ejection the ventricle continued to shrink as the result of buckling and mitral regurgitation *(C,D E)* Postoperatively the rate of contraction was rather uniform throughout systole (see key in *Fig 8*)

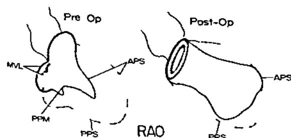


Fig 7 Line diagrams of ventriculogram RAO view (Case I) *Left diagram* preoperative view *Right diagram* postoperative view *Dotted lines* = time of mitral closure *solid lines* = end systole *Heavy lines* = plane of mitral leaflets *APS* = anterior papillary site *PPS* = posterior papillary site *PPM* = posterior papillary muscle

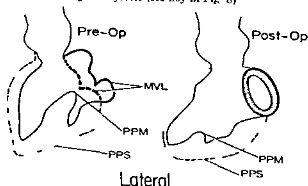


Fig 8 Line diagrams of ventriculogram left lateral view (Case I) *Left diagram* preoperative *Right diagram* postoperative view Legend as in *Fig 7*

a left anterior oblique view which was not repeated but helped identify movement of the anterior leaflet The following description is for ventricular behavior during a sequence of sinus beats The findings were exaggerated after a PVC and were not present during the ectopic contraction itself which however considerably increased mitral regurgitation With sinus beats mitral regurgitation was mild to moderate Left ventricular diastolic pressure was normal even after angiography Diastolic movement was unremarkable No aortic regurgitation was seen on supravalvular injection Coronary arteries appeared normal

Preoperatively at the onset of systole both leaflets closed in a moderately prolapsed position

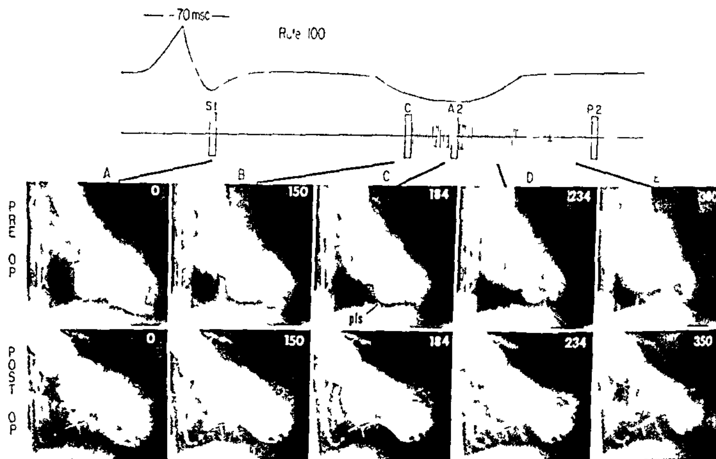


Fig 5 Ventriculogram (Case I) Right anterior oblique view Sequential frames from pre and postoperative studies related to the preoperative ECG and phonocardiogram which are diagramed above *Frame A* = mitral closure point *Frame B* = click point *Frame C* = time of aortic closure *Frame D* = maximal mitral prolapse *Frame E* = one frame before onset of diastole Number above each frame equals milliseconds after mitral closure *pls* = posterior leaflet sinus In the phonocardiogram abbreviations are the same as in *Fig 4* Validity of preoperative angio phono correlation is discussed in text General comparison of the time patterns of ventricular contraction before and after surgery was possible because heart rates were very similar But slight differences in preejection period and a 50 msec prolongation of left ventricular systole postoperatively make it inappropriate to do frame for frame comparison After surgery there was hypokinesis of the trabeculae in the apical extensions of both papillary root systems (see key in *Fig 7*)

on the inferior wall commonly about 2/3 (1/2 to 4/5) the distance between the annulus and the apex often however it is considerably back rooted or has independent heads inserting higher The anterior papillary site is often a more discrete area on the anterior lateral wall also about 2/3 the way to the apex In general the major portion of the root systems of the papillary muscles extends apically melding with each other and with adjacent trabeculae carneae Thus on anatomical grounds one would expect that buckling of the posterior papillary site would retract the inferior wall while buckling of the anterior papillary site would retract the anterior-lateral wall Transmission of papillary stress along lines of the root systems would widen this zone especially toward the apex

Our previous experience had established the importance of multiple projections in the study of mitral prolapse The right anterior oblique (RAO) projection gives an excellent view of the anterior and often the posterior papillary site But for differentiation of the anterior and posterior leaflet one must use the left lateral or half axial projection The left lateral projection also provides the best view of the posterior papillary site The lower part of the C shaped posterior leaflet sinus is well seen in both RAO and lateral views between the posterior papillary muscle and the mitral annulus In the present study we used a combination of the RAO and left lateral projections

Left ventriculography was done three times (a) ten days before, (b) nine days after, and (c) six months after surgery Angiography performed elsewhere two years previously was available for comparison with the preoperative study and in the RAO view appeared identical It also supplied

systole with much of its contents displaced into the bulging valve the ventricle seemed almost trying to turn inside out The only areas which did no contract in this jerky exaggerated way were the septum (seen best in the LAO view) and the high anterior wall adjacent to the septum (best seen in the lateral view) Anatomically these are the only areas where the trabecular network and extensions of the papillary root systems do not reach During the last 100 msec of ventricular contraction the aortic valve was closed Blood stopped going out the aorta but large quantities were transferred to an expounding pouch of mitral prolapse and into the left atrium (Figs 5 and 6C D E)

Early postoperatively the ventriculogram was strikingly different (Figs 5 6 7 and 8) Unusually close comparison was made possible by a fortunate coincidence heart rates were very similar during pre and postoperative studies RAO view cycle length pre op 0 60 post op 0 66 Lateral view cycle length pre op 0 68 post op 0 68 But even to cursory inspection the changes were obvious The frantic late systolic movement was gone the time pattern of contraction was now evenly distributed through systole From the papillary muscle sites along the apical projection of their root systems both the anterior and the inferior wall were hypokinetic furrowed by inert trabeculae carneae The predominantly apical abnormalities were best seen in the RAO projection These abnormalities were little changed when the study was repeated six months later The high anterior wall adjacent to the septum and the posterior wall between the posterior papillary site and mitral annulus were the only areas with a normal amount of movement The latter area no longer bulged in early systole The ejection fraction (calculated from the RAO view) was reduced from nearly 90 per cent to 55 per cent One might have suspected that ome surgical accident had damaged the coronaries but coronary arteriograms remained normal as did diastolic pressure (even after loading with contrast medium)

Thus the exact areas which appeared most hyperkinetic preoperatively showed loss of motion postoperatively while areas of normal contractility remained the same after surgery Also the midsystolic jerk of the ventricular wall paralleling the second rapid phase of leaflet prolapse disappeared with removal of the valve

Later suspecting that papillary muscle contraction might also have been impaired by abnormal systolic stress we carefully re evaluated the preoperative study and confirmed a previous impression Despite reports to the contrary[1] an ordinary ventriculogram is not suitable to gauge papillary muscle contraction High resolution *coronary arteriography* however may be more useful Our studies showed a small terminal branch of the obtuse marginal artery which moved quite unlike the surface or the septal vessels—or anything seen in control angiograms (Fig 9) During systole while the other arteries were developing increased angularity and moving closer together this small vessel oriented in the plane of the anterior papillary muscle moved steadily toward the base of the heart in a very distinctive way In midsystole the rate of movement suddenly increased the vessel jerked upward toward the mitral annulus appearing to straighten and probably to elongate during the second more rapid phase of movement * Fortunately ventriculograms were available at exactly the same heart rate Thus it was possible to prove that the sudden jerk of the papillary vessels coincided with the onset of buckling In the postoperative film after untethering of the papillary muscle the same vessel appeared closely coiled and shortened to 1/5 its previous length with no systolic movement Therefore we believe that we were seeing evidence of *late systolic elongation* of the anterior papillary muscle during buckling—demonstrated by the behavior of its arterial supply

To a lesser extent the surface coronaries over the *anterior papillary* site showed the same abnormal movement as the endocardial surface And at surgery systolic dimpling in this area was confirmed and recorded on movie film

Epicardial mapping of ventricular ectopic beats[3] (Fig 2) At surgery bipolar electrodes with leads 2 mm apart were methodically placed in 11 areas of the left ventricle beginning with the high anterior wall 1 cm lateral to the septum ending with the inferior wall a similar distance from the posterior septum Three parallel rows of recordings were made The final row included what was thought to be the external projection of the posterior papillary site where the recording

*The elongation chiefly involved the proximal part of the vessel. If at autopsy one retracts a papillary muscle the give is chiefly in its spring like root system

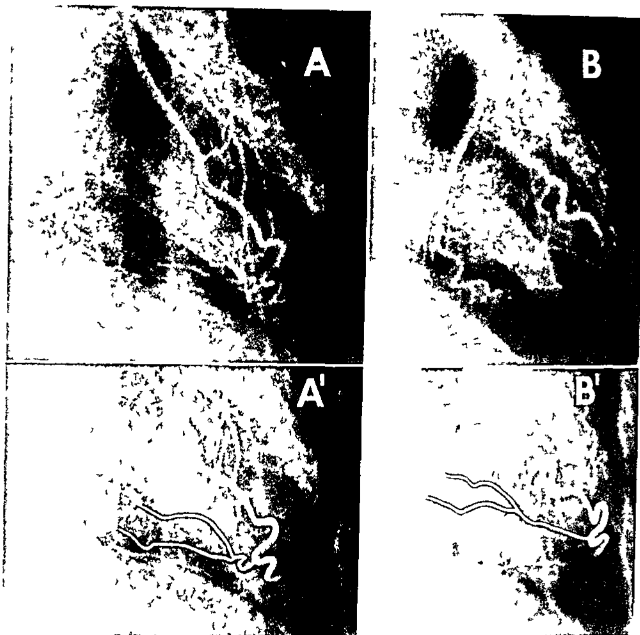


Fig 9 Coronary angiogram (Case I) *A* at mitral closure point (corresponds to frame A in *Figs 5* and *6*) *B* at nearly maximal mitral prolapse (corresponds to frame D in *Fig 6*) The frames below have been retouched to show the outline of the vessel feeding the anterior papillary muscle At the click point with the onset of buckling this vessel suddenly jerked inward and elongated (*see text*)

(Figs 5*A* 6*A*, 7 and 8) The prolapse steadily increased as contraction progressed Yet midway through systole, with the valve obviously bulging, the ventricle apart from protrusion of the inferior wall in the area of the posterior leaflet sinus, appeared normal (Figs 5*B*, 6*B*) Then very suddenly, coincident with the click and the point of complete leaflet disengagement (Fig 6*B*) very abnormal *simultaneous* movements of the valve and ventricle began (1) The rate of prolapse of the leaflets suddenly increased producing a second very large phase of movement and initiating mitral regurgitation (2) The rate of ventricular emptying abruptly accelerated so that a jerky biphasic emptying pattern was produced

With the onset of the second phase of prolapse both leaflets suddenly exploded into a cauliflower shaped protuberance, bulging furiously between sites of chordal attachment (Fig 6 *C D*, *E*) The foci of abnormal ventricular movement appeared to be just above and below the cardiac apex corresponding to the papillary sites Movement of the posterior papillary site occurred in an unusual arc not just inward but also sharply upward toward the mitral annulus In the lateral view the tip of the posterior papillary muscle (a conical filling defect) could be seen actually entering the mitral ring (Fig 6*C D E* and Fig 8) Emptying was remarkably complete nearly 90 per cent during a sequence of sinus beats At end

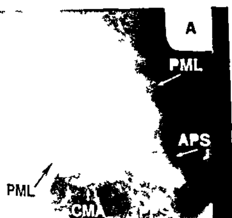


Fig 10A. Case III End systole RAO view preoperative view The left ventricle apparently retracted at both anterior and posterior papillary sites (*APS* and *PPS*) flares above into a dilated calcified mitral annulus (*CMA*) part of which is seen through contrast medium at inferior border The prolapsing mitral leaflets (*PML*) bulge into the atrium

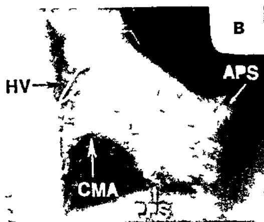


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Case III A woman age 75 seen 16 years earlier for palpitation and atypical chest pain was found in 1974 to have developed a heavy shelf of annular mitral calcification (verified at operation) atrial fibrillation and congestive heart failure Though congestive symptoms were easily controlled with minimal therapy she remained very weak apparently as a result of a low fixed cardiac output The first phonocardiogram in 1958 showed findings quite similar to those of Case I a late systolic bridging murmur initiated by a click shortening of the Q A 2 time and equivalent wide splitting of S 2 (50 to 60 msec) In 1975 the murmur had become pansystolic but still prominently bridged S 2 which remained widely split the Q A 2 interval however was nearly fixed (at 0 31 sec) over a wide range of heart rates and there was no distinguishable click Clinically proper timing was difficult because A 2 was unnaturally soft and buried in the murmur During the first 72 hours after mitral replacement S 2 progressively closed and A 2 rapidly increased in intensity The mitral annulus was unusually large easily accepting a 31 Hancock prosthesis Angiographically the valve was enough thickened to be seen easily both in systole and diastole as a negative shadow in the contrast medium Apparently as a result of the projecting annular shelf the leaflets never reached the normal diastolic station but remained abnormally high transverse and persistently visible * Beginning systole severely disengaged they almost immediately entered a large rapid phase of prolapse which flattened the posterior leaflet against the atrial wall and was accompanied by a corresponding quick ventricular movement Prolapse was maximal within 50 msec and apparently resulted in moderately severe mitral regurgitation which helped drain the ventricle further The left atrial V wave was 26 mm the left ventricular end diastolic pressure was normal The ventriculograms at end systole were almost superimposable on those in Case I Postoperative changes were also quite similar with considerable decrease in ejection fraction and aneurysms at both papillary sites (Fig 10) Gross and microscopic pathology also closely resembled that in Case I except for significant fibrosis of both papillary muscles (larger spec

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Additional surgical cases

Case II A woman 59 years old, who also had only moderate chiefly late systolic mitral regurgitation, normal intracardiac pressures, and normal coronary arteries, was operated upon after several near fatal episodes of ventricular fibrillation recurring despite combined propranolol and diphenylhydantoin therapy During an 18 month postoperative follow up, previously inverted T waves have normalized and arrhythmias have not recurred By phonocardiogram the murmur began early without a definite click but as in the first case bridged A 2 Splitting of S 2 and shortening of Q A 2 time not apparent with the patient recumbent increased to 60 msec during sitting and standing but became normal postoperatively At surgery the mitral annulus was remarkably dilated easily accepting a 33 mm Hancock prosthesis Pathologically the striking difference from Case I was quite severe papillary muscle fibrosis the leaflets (especially the posterior) were also considerably more voluminous and diffusely myxoid, and the chordae were longer The preoperative ventriculogram showed less mobility of the valve curtain and less protrusion into the atrium than in Case I There was no exaggerated ventricular emptying ejection fraction was 45 per cent But there was clearly the same arc like movement of an indentation of the posterior papillary site (seen only in the lateral view) This seemed to pull behind it a portion of the heavily trabeculated wall of the posterior leaflet sinus In the RAO view apparently just proximal to the anterior papillary site was a curious sac like protrusion which looked almost stinted as the surrounding ventricle clamped down around it In diastole there was abnormally rapid early relaxation in a hyperkinetic area apical to the anterior papillary site the only clue to the flimsy states of its musculature[1] Postoperatively there was little reduction in over all ventricular emptying But the posterior papillary site no longer arced upward toward the mitral annulus. There was virtual akinesis of large convoluted trabeculae in the posterior basal wall In the RAO view previous buckling of the ante-

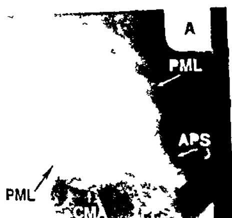


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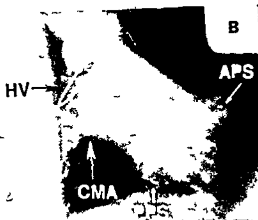


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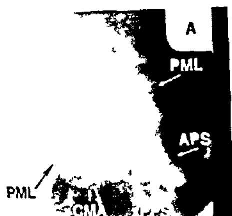


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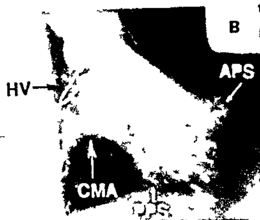


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imens were available) Anterior leaflet involvement was obvious Chordae were definitely not elongated Seen at surgery the papillary muscles appeared remarkably long and thick, and trabecular hypertrophy was striking Ten months postoperatively the patient is much improved and requires no cardiac drugs except digitalis

Case IV A 70 year old woman had stopped teaching school 15 years previously because of exertional palpitation and chest pain associated with a 'creaking' heart murmur Six months before admission she had developed congestive heart failure and multiple syncopal episodes due to ventricular fibrillation The murmur was musical and found to last 3/4 of systole Phonocardiographic studies were not done but wide splitting of S 2 was noted clinically An echocardiogram showed pansystolic prolapse of both leaflets which anatomically proved to be aneurysmal, abnormally vascularized and diffusely myxoid with intact but elongated chordae The ventriculogram showed severe mitral regurgitation, marked prolapse of both leaflets, an ejection fraction of 60 per cent and curious stinted projections proximal to both papillary sites similar to those in Case II Four months postoperatively the ventricular cavity was considerably enlarged and emptying was markedly reduced, aneurysms of both papillary sites were seen Eighteen months later congestive heart failure was worse and the ejection fraction had further deteriorated to 20 per cent An attempt to stop propranolol/diphenylhydantoin therapy at that time resulted in ventricular fibrillation, from which she was resuscitated Medication was resumed and arrhythmias have not re occurred

Unoperated cases

Case V A 34 year old woman with palpitations and atypical chest pain was found to have a short bridging murmur 60 msec splitting of S 2 with equivalent abbreviation of Q A 2 time and severe prolapse of both leaflets by echocardiogram T waves were inverted sharply in Leads III aV$_F$ and partly in II and V_6 Fourteen months later she remains well

Case VI A 43 year old woman with the same clinical findings had had brief episodes of complete syncope for about 10 years but refused further study

Case VII A 56 year old woman with the same auscultatory findings but only borderline T wave abnormalities had a five year history of anginoid chest pain exercise aggravated ventricular ectopy and one convulsive seizure Four years later her effort tolerance was reduced, the brief murmur had become pansystolic and cardiac catheterization showed normal coronaries but severe mitral regurgitation with a V wave of 40 mm

Case VIII A woman aged 36 with a bridging murmur, a click very close to S 2 and 90 msec shortening of Q A 2 time developed paroxysmal atrial fibrillation 12 years later with no change in auscultatory findings and still normal ECG

Case IX A man aged 33 with no significant symptoms was found to have a late systolic bridging murmur and 65 msec splitting of S 2 The ventriculogram was similar to that of Case I Nine years later he developed atrial fibrillation The murmur had become pansystolic still bridging A 2 The ventriculogram showed much worsened mitral regurgitation but less protrusion of the leaflets into the atrium and less marked buckling of the ventricle T waves remained normal

Case X A man aged 53 was followed for 1½ years during the course of Hodgkin s disease for which he received no chemotherapy 60 msec splitting of S 2 was constant and persistent even on standing A late systolic murmur was variable and often absent The electrocardiogram showed no T wave abnormality At postmortem there were severe myxomatous aneurysms of both leaflets and extensive cross striated papillo trabecular fibrosis with sparing of the subjacent ventricle

Case XI An 18 year old football lineman without click murmur, or angiographic mitral regurgitation had 60 to 70 msec splitting of S 2 persistent during standing shortening of both LVET and PEP severe middle and medial scallop prolapse (shown angiographically but missed by echo), paroxysmal ventricular tachycardia and episodes of syncope triggered by effort or excitement Attacks ceased on propranolol

Case XII A vigorous 31 year old male with findings very similar to Case I (100 msec split of S 2 a short murmur nearly symmetrically bridging A 2 and multiple PVC s despite propranolol) died suddenly following a tennis game Marked myxomatous involvement of both leaflets was

confirmed at autopsy. Papillary muscles were large but only minimally fibrotic.

Discussion

Mitral valve replacement for life-threatening arrhythmias has not been previously reported. The success of surgery in Case I was certainly not complete. In spite of a favorable initial postoperative course, freedom from ectopy at rest, and gradual normalization of T waves, it appears that satisfactory long-term suppression of exertional arrhythmias may require a combination of propranolol and diphenylhydantoin—therapy never used preoperatively and shown by Pocock and Barlow[8] to be superior to propranolol alone. Surgical benefit in Case II, however, seems undeniable. 18 months after mitral valve replacement for intractable episodic ventricular fibrillation, she has no arrhythmias and takes no drugs. A third patient of the same type has had a successful operation at Rochester, New York.

The experience in Case IV suggests that it is unwise to stop previously required antiarrhythmic therapy when mitral valve replacement has been done for congestive heart failure. Certainly, it would appear that if surgery has a place, it is for those rare persons who continue to have life-threatening arrhythmias despite combined propranolol-diphenylhydantoin therapy. In our experience, chest pain associated with arrhythmias often responds better to combined therapy than to propranolol alone. For isolated chest pain, however intractable, we have hesitated to advise surgery. Valve replacement is a drastic step. Pain in the absence of arrhythmias does not seem to be life threatening and furthermore may be indistinguishable from that found in many persons without prolapse. The LeWinter test[7] has sometimes given us confusing results, failing to duplicate the pain in patients with severe prolapse and eliciting discomfort when angiographic evidence was absent or minimal.

The present studies support the concept of buckling. After mitral valve replacement all four cases developed decreased ventricular emptying and aneurysms of the papillary sites, which in two cases had previously been foci of hyperkinesis. The time pattern of ventricular movement, which had followed that of the valve, was also drastically changed. This sequence has never been duplicated in our experience with rheumatic heart disease and seems best explained by untethering of the ventricle from the mitral prolapse. Neither of two alternate explanations seems totally acceptable.

1. It seems possible that loss of the low-resistance atrial spillway after correction of mitral regurgitation may reveal previously inapparent ventricular dysfunction. This, however, would not explain either the degree or the focal nature of the changes observed.

2. Surgical injury seems an unlikely cause of these almost stereotyped postoperative abnormalities. In none of the cases was the apex vented. Coronaries remained unchanged. We believe that untethering the ventricle by mitral valve replacement may sometimes lead to horizontal transverse fiber disruption just proximal to the papillary muscles, but the angiograms here suggested more distal damage. Furthermore, there were clues to pre-existing hypofunction. (A) In Case I the anterior papillary muscle—fortuitously outlined by its vascular pattern during coronary arteriography—seemed to elongate in late systole. (B) In Case II there was abnormally early diastolic relaxation[1] in areas later proved to be hypokinetic. (C) Papillary fibrosis was also found—moderate in Case III, severe in Case II. Thus, there was probably antecedent damage of the papillary muscles and their root systems concealed by inward traction from the prolapsing leaflets and by late systolic unloading of the ventricle. These findings helped to confirm the belief that harmful inward tensions on the papillary sites may develop as the result of mitral prolapse. Postoperative electrocardiographic improvement in three of four cases implies that some of these effects may be reversible.

In Case I the link of the buckled posterior papillary site to the arrhythmias seems clear since preoperative study and intraoperative mapping showed that the ectopic focus was at or very near the deformed area. The mechanism of the arrhythmias may be similar to that in ventricular aneurysm, where recent mapping studies have suggested that traction on adjacent viable muscle is the source.[12] The irritable focus was of course not excised; perhaps its continued presence helps explain the recurrent arrhythmias after surgery. The finding that gentle external pressure over the posterior papillary site temporarily stopped the arrhythmia shows the importance of subtle

alteration in local myocardial tension, and may suggest a re entry mechanism for the ectopy Criley and colleagues[8] have described two vector cardiographic patterns for ventricular ectopic beats associated with mitral prolapse[6], one of these probably originates higher on the ventricle than either the focus in the present case or the external projection of the main papillary muscle trunks Yet, even if ectopy results entirely from stress lesions in one or both papillary sites perhaps precise vectorcardiographic correlation should not be expected Basal extension of the papillary root systems and lateral spread of muscle damage into the trabeculae (documented in our own autopsy material) would provide a wider and not altogether predictable arrhythmogenic zone In successfully operated Case II there were four different PVC forms

Even with the angiographic evidence presented here it may be difficult to believe that ventricular contraction can be distorted and emptying strikingly increased by attachment to a billowing valve Our anatomical studies have suggested that mitral prolapse by producing disengagement and malposition of the leaflets can generate much abnormal sail tension [1,2] Theoretically this should peak (A) When the normal keystone effect is lost and disengagement is complete (B) *As the leaflets escape from their normal protected* position and become more perpendicular to the force vectors developed during aortic outflow This extra sail force being concentrated ultimately on the papillary sites might under certain circumstances enhance their inward and basal movement which in turn would further increase prolapse Yet this schema hardly explains the remarkable increase in ventricular emptying seen in cases I and III Two other factors probably play a role (A) A distortion of intracardiac flow (discussed below) (B) Systolic unloading [23] Some unloading may have occurred early in systole as the result of intravalvular regurgitation into the sunburst of leaflet prolapse But the large ventricular buckling motion started only as transvalvular leakage decompressed the chamber By contrast, the papillary muscle was certainly *not* unloaded but (as documented in Case I) apparently elongated during ventricular buckling probably as the result of rapidly increasing systolic stress If late systolic papillary movement was paradoxical, it seems likely that early systolic contraction was also poor or absent This idea is supported by the fact that there was more angiographic evidence of prolapse, even in early systole, than could be explained by anatomical redundancy Thus defective papillary contraction may be common in severe mitral prolapse whether as a primary event or from *focal stress induced myocardiopathy*

Another significant objection to the buckling theory is the considerable variation in ventriculograms among patients with idiopathic mitral prolapse Although Grossman and associates[10] originally described areas of increased motion others have encountered a wider range of abnormality [4,25] Certainly, exaggerated emptying occurs only in a minority Yet perhaps one should not expect the ventriculographic effects of increased papillary stress to be stereotyped Significant factors probably include (1) the number and size of the involved leaflet segments (2) the length of the chordae and leaflets, (3) the size of the mitral annulus (4) the extent and depth of myocardial damage, (5) variations in the papillary root systems, (6) the duration of the process, and (7) the amount and the timing of the unloading effect of mitral regurgitation Furthermore, because of the difference in location of the two papillary sites, their abnormal movements may not be seen with equal ease buckling in the *area of the anterior papillary muscle occurs* almost in the direction of normal apex to base shortening, which therefore may simply appear enhanced By contrast the posterior papillary muscle, pulled superiorly by the prolapsing leaflet makes a more noticeable dent on the ventricular cavity With these facts in mind the ballerina foot and the hourglass (or cavity obliteration) patterns as described by Scampardonis and co workers [4] seem adequately explained as buckling of the posterior or of both papillary sites respectively Bulky papillary muscles probably create much of the deformity which may at times persist in diastole

But there are two other common patterns which are not obviously attributable to buckling

1 Defective long axis shortening or decreased inferior wall motion the chief anomalies in 25 per cent of Scampardonis s patients (often in our experience associated with angiographic evidence of considerable trabecular hypertrophy) probably result from more profound damage to myocardial loops involving the anterior and

posterior papillary sites respectively Serial angiograms in some of our cases distinctly suggest that the degree of buckling and of prolapse may sometimes diminish as the patient deteriorates and mitral regurgitation increases The postoperative changes in Case II show that lack of exaggerated emptying does not necessarily preclude buckling which may still animate a non contractin papillary root system Here also unusual dilatation of the mitral annulus apparently absorbed much of the mitral redundancy and minimized projection of the severely aneurysmal leaflets into the atrium If the pathology in Case II is representative reduced ventricular emptying in the presence of other signs of marked ventricular involvement may sometimes mean more severe damage a wider mitral annulus larger more fibrotic papillary muscles and probably more papillo trabecular dysfunction In coronary artery disease we believe that we have also seen localized retraction in the middle of hypokinetic wall segments (which theoretically could also be a source of arrhythmias)

2 A normal ventriculogram common in our experience was found in 20 per cent of Scampardonis's patients and also in two fatal cases one of whom had significant papillary and ventricular fibrosis [4] Although there is no reason why increased papillary stress should always produce ventricular deformity (especially in the common type of *prolapse* which may involve only one scallop of the posterior leaflet) these findings may partly reflect the limitations of present day angiography Using the left anterior oblique half axial projection we have demonstrated buckling beautifully when it was inapparent on conventional views The experience *in* Case II also suggests that buckling may sometimes be appreciated best in retrospect after mitral valve replacement

Severe mitral prolapse sometimes seems capable of producing peculiar hemodynamic changes as exemplified in Cases I II and III Disproportionate shortening of the left ventricular ejection time is a cardinal finding often with evidence of significant emptying after forward flow has ceased It seems possible that two factors may be operative (1) The often sudden late systolic steal of ventricular blood by additional prolapse and mitral regurgitation (2) A curious rerouting of systole In Case I there appeared to be preferential flow toward the prolapsing valve In fact the amount of blood diverted into the inflow tract seemed to be more than could readily escape into the atrium this area including the posterior leaflet sinus bulged prominently until midsystole producing a pot bellied appearance (Fig 5A *B C*) and finally moved inward only when decompressed by mitral regurgitation (Fig 5*D F*) Postoperatively the bulge–collapse sequence was not present There may be anatomic reasons for this apparent rerouting of systole concomitant prolapse of the anterior leaflet removes the normal shield between the inflow and outflow tracts of the left ventricle allowing blood propelled toward the base of the heart free entry into the posterior leaflet sinus Such diversion of flow might help to produce the ventriculographic appearance of postero basal hypokinesis and ultimately lead to permanent dilatation in this area and of the mitral annulus In Case I the abrupt onset of mitral regurgitation and buckling quickly decompressed this area But then precipitous movement of the papillary sites toward the mitral annulus helped further to deflect blood away from the aortic exit—very likely most of the apical and inferior contents of the left ventricle

Clinical findings in the seven unoperated patients are also compatible with abnormally fast left ventricular ejection or usurpation of late systole This unusual syndrome includes

1 Frequent significant involvement of the anterior as well as the posterior leaflet (seen in one of the three catheterized cases and in echocardiograms which were available in three others)

2 A *widely* split S 2 usually with equivalent shortening of the Q A 2 time (but often normal PEP) When A 2 is easily heard the widely separated P 2 may be confused with an opening snap Unlike the usual split S 2 this is not narrowed with standing It seems distinct from the occasionally heard diastolic click which in other cases we have correlated with abnormally rapid piston like early diastolic descent of a severely buckled probably quite hypokinetic posterior papillary site Wide splitting of S 2 has been known to connote severe often acute mitral *regurgitation* but not mitral prolapse with intact chordae splitting of 100 msec has not been previously reported in mitral valve disease

3 A bridging murmur (if mitral regurgitation occurs) This is very likely to be mistimed because A 2 is buried and may sometimes be unusually quiet *probably* as a result of the curious under

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found that fibrosis correlated best with the patient's age. Thus it appears probably to be the end stage reaction to a long standing physiologic lesion. In some cases (e.g. Case X) the arrangement of fibrosis in bands perpendicular to the fiber axis seems compatible with over stretching changes.

While the present results do not solve the primary problem they seem to demonstrate the effects of abnormal papillary and ventricular stress produced by severe mitral prolapse. Our findings also support the general hypothesis that tethering of the ventricle to the mitral annulus may significantly affect cardiac function. In diastole a shortened rigid chordo-papillary apparatus probably may interfere with ventricular filling independently of valvular or subvalvular mitral stenosis. The mere presence of the mitral apparatus may help to prevent undue diastolic dilatation. In systole when there is disengagement of the mitral leaflets increased sail traction on the heart's internal rigging may stabilize the left ventricular wall and particularly when afterload is reduced by mitral regurgitation actually augment ventricular emptying. Some of the baffling left ventricular dysfunction which sometimes develops after mitral valve replacement may be due to loss of these mechanisms.

Summary

Because of intractable ventricular arrhythmias after a near fatal episode of ventricular fibrillation a patient with idiopathic mitral valve prolapse was subjected to mitral valve replacement. Vector analysis and intraoperative epicardial mapping localized the ectopic focus to the region of the posterior papillary muscle. The patient is alive and well two years after surgery. Chronically inverted T waves have become upright. But propranolol and diphenylhydantoin are needed to prevent arrhythmias and T wave abnormalities during standing and exercise. Preoperatively with the onset of mitral regurgitation and a second rapid phase of prolapse the ventriculogram was deformed by abnormal mid systolic hyperkinesis at both sites of papillary muscle insertion. Postoperatively focal hypokinesis appeared in the same areas implying that they had been retracted by the prolapsing valve. Preoperatively a papillary tip could be seen entering the mitral ring while coronary arteriography showed late systolic elongation of a small vessel feeding the anterior papillary muscle suggesting that the papillary apparatus was indeed subject to damaging stress during the abnormal basal movement. Three other persons with severe mitral prolapse (but intact chordae) have had valve replacement and developed qualitatively similar changes in the ventriculogram. Papillary specimens in two showed significant fibrosis. Indication for operation in one of these was episodic ventricular fibrillation which has not recurred. A spectrum of ventriculographic abnormality associated with mitral prolapse could be partly explained by hypokinesis of the papillary loops variably disguised by retraction stress transmitted from the billowing leaflets translocation of blood into the expanding valve sail and various degrees of unloading into the left atrium. Abnormal intraventricular flow may probably result from associated prolapse of the anterior leaflet and from buckling of the papillary sites toward the mitral annulus. Unusual physical findings in the operated cases and in eight other patients define a clinically recognizable syndrome in which severe prolapse abbreviates left ventricular ejection. Liability to symptoms and to progression of disease seems high in this group.

Grateful acknowledgement is made to Dr. F. D. Maner and Dr. C. W. Beeson II for referral of the first patient and extensive use of their records, the 19?1 cardiac catheterization and an echocardiogram and phonocardiogram done in the late postoperative period.

The second and third operated cases were studied through the courtesy of Dr. P. H. Robinson and Dr. F. R. Dorney.

Clinical information on Case XII was kindly made available by Dr. David Ferling and Dr. Alan Faulk.

REFERENCES

1. Cobbs, B. W., Jr.: in J. W. Hurst and R. B. Logue eds. The heart. New York, 19?0, McGraw-Hill Book Company, Inc., pp 813-14, 818-21.
2. Cobbs, B. W., Jr.: in J. W. Hurst ed. The heart. New York, 19?4, McGraw-Hill Book Company, Inc., pp 8?4-5, 881-89.
3. Behar, V. S., Whalen, R. E., and McIntosh, H. D.: The ballooning mitral valve in patients with the "precordial honk" or "whoop." Am J Cardiol 20:89, 196?.
4. Pocock, W. A., and Barlow, J. W.: Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome. Analysis of a further 130 patients with a late systolic murmur or nonejection systolic click. Am J Med 51:31, 19?1.
5. Jeresaty, R. M.: Mitral valve prolapse-click syndrome. Progr Cardiovasc Dis 40:633, 1973.
6. Criley, J. M., Zeilenga, D. W., and Morgan, M. T.: Mitral dysfunction: A possible cause of arrhythmias in the prolapsing mitral leaflet syndrome. Trans Am Clin Climatol Assoc 85:44, 1973.
7. LeWinter, M. M., Hoffman, J. R., Shell, W. E., Karliner

mining by which ejection is terminated Bridging of S 2 may not be a specific finding and probably is likely to occur whenever resistance to filling of the left atrium remains low in late systole The phenomenon has also been noted by Barlow and colleagues[27] in mitral prolapse But marked bridging in conjunction with abbreviated ejection cannot be explained by conventional hemodynamics

4 Unusually complete ventricular emptying at least in the early stages of the syndrome

5 A systolic click in quite close and fixed relation to S 2 (in some cases) These findings except for minor abbreviation of Q A 2 time (< 40 msec) and somewhat wide splitting of S 2 were not seen in 30 control patients with mitral prolapse including some with severe and symptomatic disease In Cases X and XI with no murmur and wide splitting of S 2 there was probably little if any mitral leak While the commodious leaflets could have provided a sort of intravalvular regurgitation it seems probable that ejection was also shortened by other factors—including perhaps the inotropic effect of early systolic unloading ' and of retraction forces In any case recognition of this less common syndrome may identify one group of patients at higher risk both for progression of mitral regurgitation and for manifestations of increased valve stress

The primary abnormalities producing idiopathic mitral prolapse still elude description As Barlow and associates noted among their original papers, there is obviously more than one etiology Primary myxoid degeneration of the leaflets is probably the cause in many cases, especially in Marfan s and the floppy valve syndrome, ' and in patients with a family history, ' chest wall deformity, or tricuspid involvement " Our experience however shows that severe prolapse may occur without elongation of major chordae and with only moderate increase in leaflet area Pathologic findings, especially in Case I were those which might have been expected if the leaflets prolapsed because of poor papillary support Collagenous thickening was as striking as myxomatous degeneration, grossly the leaflets appeared 'calloused Similar myxo collagenous change confined to the medial half of both leaflets has been found in children with atrial septal defect ' distribution which we *believe strongly* suggests that mitral prolapse in this setting results from dysfunction of the posterior papillary muscle, which perhaps may be functionally incorporated into the abnormally moving septum

Thus, it seems likely that abnormalities of ventricular or papillary contraction can be the primary event in some idiopathic cases (a) Ranganathan and Burch[11] have pointed out that papillary muscles probably naturally have a rather precarious blood supply Perhaps subclinical myocarditis may leave its ultimate scars mainly in these vulnerable areas— mitral papillitis ' The clinical histories in some of our patients distinctly suggest this possibility (b) Perhaps the process may also begin as a subtle electrophysiologic disorder a chronic inotropic state (faster or more complete contraction of the ventricle than of the papillary muscles), or a change in the sequence of myocardial depolarization Delayed contraction of the left ventricular inflow tract would distort intracardiac flow and leave the posterior leaflet abnormally exposed A papillary muscle contracting out of order could allow mitral prolapse An alternate electrical pathway might also help explain re entrant ventricular arrhythmias (c) Studies of papillary muscle physiology by Armour and Randall[11] suggest previously unrecognized opportunities for both primary and secondary dysfunction The papillary muscle is only part of a myocardial fiber loop with both ends anchored at the mitral annulus[11] In the dog although the papillary muscle normally depolarizes first it does not begin to contract as soon as the epicardium ' Thus sail traction from a prolapsing leaflet might be applied to the papillary muscle *before* the onset of its contraction—at a time perhaps when a Starling effect could still be produced Furthermore stimulation of cervical sympathetics at various levels can produce segmental changes in contractility actually increasing activity of one papillary muscle without much affecting the other ' Contraction disorders of the papillary loop thus seem possible reponses to physiologic stimuli and perhaps may provide a model for the contraction ring ' proposed by Grossman and associates ' It seems unlikely, however that papillary contraction could remain long unimpaired in severe mitral prolapse Yet papillary fibrosis as shown by Cases X and XII does not necessarily correlate with symptoms or with electrocardiographic abnormalities In a study of papillary muscle from eight cases of severe mitral prolapse we

The narrow aortic annulus

A technique for inserting a larger prosthesis

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Obstruction to forward flow in prosthetic aortic valves with a central occluder occurs at one or more of three sites[1] at the valve ring—inflow or primary orifice, at the truncated cone (frustrum) from the circumference of the valve ring to the perimeter of the occluder in the open position—outflow or secondary orifice, and between the perimeter of the occluder and the surrounding tissue—tertiary orifice. Secondary and tertiary orifice obstructions have largely been eliminated by the use of eccentric monocusp central flow prostheses (Bjork-Shiley, Wada-Cutter, Lillehei-Kaster) but obstruction at the valve ring, although partly alleviated by the improved functional characteristics of these prostheses, remains an obstacle to the complete hemodynamic correction of aortic valve disease when this is associated with a small aortic annulus.

In this paper a technique is described for inserting a prosthesis with a larger valve ring than that which would normally be possible for the dimension of the host aortic annulus.

Method

The surgical technique is illustrated in Fig. 1. A standard oblique aortotomy is performed (Fig. 1A). The aortic valve is excised and the aortic annulus is measured with an obturator. If it precludes the insertion of a 21 mm. Bjork-Shiley valve (?3 mm. in larger patients), the aortotomy is continued across the aortic annulus for approximately 0.5 to 1.0 cm. (Fig. 1B) immediately anterior to the insertion of the medial commissure of the mitral valve into the ventricular septum. As the conduction system is located further anterior in the muscular ventricular septum along its junction with the membranous septum, damage to this structure and the mitral valve is avoided. Care must also be taken to avoid opening the right atrium which is firmly adherent to the left ventricular outflow tract below this point. Sutures are then inserted into the aortic annulus but only in the regions corresponding to the left and right coronary cusps (Fig. 1C and D). These same sutures are passed through the prosthetic valve ring and should involve approximately one half of its circumference. The broad end of a tear-drop shaped pericardial patch, 1.5 to 2.0 cm. at its widest dimension, is sutured to the lower end of the incision and continued upwards for approximately one third of the length of the aortotomy on either side (Fig. 1E). It is at this stage only that the prosthetic valve is tied into position by the sutures which had previously been inserted through the aortic annulus (Fig. 1F). The remaining one half of the prosthesis is sutured to the pericardial patch and adjacent aortic wall by multiple horizontal mattress sutures placed from the *outside* inwards (Fig. 1F). The prosthesis now lies slightly obliquely and 0.5 to 1.0 cm. above the original plane of the aortic annulus in the region of the non-coronary sinus. Closure of the aortotomy is completed with the pericardial patch (Fig. 1G).

Twelve patients have been subjected to the procedure. In eight the aortic annulus was originally too small to have accepted a valve larger than a 19 mm. Bjork-Shiley but using this tech

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J S and O Rourke R A Phenylephrine induced atypical chest pain in patients with prolapsing mitral valve leaflets Am J Cardiol 34 12 1974
8 Kaufmann R and Theophile U Automatie fordernde denungseffekte und purkinjefaden papillarmuskeln und vorhoftrabekeln von Rhesus Affen Pfluegers Arch 197 174 1967 (includes summary in English)
9 Wit A L Fenoglio J J Wagner B M and Bassett A L Electrophysiological properties of cardiac muscle in the anterior mitral valve leaflet and the adjacent atrium in the dog Possible implications for the genesis of atrial dysrhythmias Circ Res 32 731 1973
10 Grossman H Fleming R J Engle M A Levin A H and Ehlers K H Angiocardiography in the apical systolic click syndrome Radiology 91 898 1968
11 Rosenbaum M B and Kezdi P ed Classification of ventricular extrasystoles according to form J Electrocardiology 2 289 1969
12 Kastor J A Spear J F and Moore E N Localization of ventricular irritability by epicardial mapping Circulation 45 952 1972
13 Dunaway M C King S B Hatcher C R and Logue R B Disabling supraventricular tachycardia of Wolff Parkinson White syndrome (Type A) controlled by surgical A V block and a demand pacemaker after epicardial mapping studies Circulation 45 522 1972
14 Weissler A M and Garrard C L Jr Systolic time intervals in cardiac disease Mod Concepts Cardiovasc Dis 40(1 & 2) 1 1971
15 Liedtke A J Gault J H Leaman D M and Blumenthal M S Geometry of left ventricular contraction in the systolic click syndrome Characterization of a segmental myocardial abnormality Circulation 47 27 1973
16 Ranganathan N Lam J H C Wigle E D and Silver M D Morphology of the human mitral valve The valve leaflets Circulation 41 459 1970
17 Marshall C E and Shappell S C Sudden death and the ballooning posterior leaflet syndrome Detailed anatomic and histochemical investigation Arch Pathol 98 134 1974
18 Wilson C S Krueger S Forker A D and Weaver W F Correlation between segmental early relaxation of left ventricular wall in coronary occlusive disease Am Heart J 89 474 1975
19 Korn D DeSanctis R W and Sell S Massive calcification of the mitral annulus A clinicopathological study of fourteen cases N Engl J Med 267 900 1962
20 Pocock W A and Barlow J B Post exercise arrhythmias in the billowing posterior mitral leaflet syndrome Am Heart J 80 740 1970
21 Ross A M and Yu P Personal communication (12/4/74)
22 Gallagher J J Oldham H N Wallace A. G., Peter R H and Kasell J Ventricular aneurysm with ventricular tachycardia Report of a case with epicardial mapping and successful resection Am J Cardiol 35 696 1975
23 Eckberg D L Gault J H Bouchard R L Karliner J S and Ross J Jr Mechanics of left ventricular contraction in chronic severe mitral regurgitation Circulation 47 1252 1973
24 Scampardonis G Yang S S Maranhae V Goldberg H and Gooch A S Left ventricular abnormalities in prolapsed mitral leaflet syndrome Circulation 48 287 1973
25 Gulotta S J, Gulco L Padmanabhan V and Miller S The syndrome of systolic click, murmur and mitral valve prolapse—A cardiomyopathy? Circulation 49 717 1974
26 Trent J K Adelman A G Wigle E D and Silver M D Morphology of a prolapsed posterior mitral valve leaflet Am Heart J 79 539 1970
27 Barlow J B Bosman C K Pocock W A and Marchand P Late systolic murmurs and non ejection (mid late) systolic clicks An analysis of 90 patients, Br Heart J 30 203 1968
28 Read R C and Thal A P Surgical experience with the floppy valve Surgery 59 1673 1966
29 Stannard M Slomen J G Hare W S C and Goble A J Prolapse of the posterior leaflet of the mitral valve A clinical familial and cineangiographic study Br Med J 3 71 1967
30 BonTempo C P Ronan J A de Leon A C and Twigg H L Radiographic appearance of the thorax in systolic click-late systolic murmur syndrome Am J Cardiol 36 27 1975
31 Gooch A S Maranhao V Scampardonis G Cha S D and Yang S S Prolapse of mitral and tricuspid valves in systolic murmur-click syndrome N Engl J Med 387 1218 1972
32 Okada R Galbov S and Leve M Relation of shunt flow and intracardiac pressures to heart valve structure in atrial septal defect Am Heart J 78 781 1969
33 Ranganathan N and Burch G E Gross morphology and arterial supply of the papillary muscles of the left ventricle of man Am Heart J 77 506 1969
34 Armour J A and Randall W C Structural basis for cardiac function Am J Physiol 218 1517 1970
35 Armour J A and Randall W C Electrical and mechanical activity of papillary muscle Am J Physiol 218 1710 1970
36 Armour J A Hageman G R and Randall W C Arrhythmias induced by local cardiac nerve stimulation Am J Physiol 223 1068 1972

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8 Kaufmann R and Theophile U Automatie fordernde denungseffekte und purkinjefaden papillarmuskeln und vorhoftrabekeln von Rhesus Affen Pfluegers Arch 197 174 1967 (includes summary in English)
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11 Rosenbaum M B and Kezdi P ed Classification of ventricular extrasystoles according to form J Electrocardiology 2 289 1969
12. Kastor J A Spear J F and Moore E N Localization of ventricular irritability by epicardial mapping Circulation 45 952 1972
13 Dunaway M C King S B Hatcher C R and Logue R B Disabling supraventricular tachycardia of Wolff Parkinson White syndrome (Type A) controlled by surgical A V block and a demand pacemaker after epicardial mapping studies Circulation 45 522 1972
14 Weissler A M and Garrard C L Jr Systolic time intervals in cardiac disease Mod Concepts Cardiovasc Dis 40(1 & 2) 1 1971
15 Liedtke A J Gault J H Leaman D M and Blumenthal M S Geometry of left ventricular contraction in the systolic click syndrome Characterization of a segmental myocardial abnormality Circulation 47 27 1973
16 Ranganathan N Lam J H C Wigle E D and Silver M D Morphology of the human mitral valve The valve leaflets Circulation 41 459 1970
17 Marshall C E and Shappell S C Sudden death and the ballooning posterior leaflet syndrome Detailed anatomic and histochemical investigation Arch Pathol 98 134 1974
18 Wilson C S Krueger S Forker A D and Weaver W F Correlation between segmental early relaxation of left ventricular wall in coronary occlusive disease Am Heart J 89 474 1975
19 Korn D DeSanctis R W and Sell S Massive calcification of the mitral annulus A clinicopathological study of fourteen cases N Engl J Med 267 900 1962
20 Pocock W A and Barlow J B Post exercise arrhythmias in the billowing posterior mitral leaflet syndrome Am Heart J 80 740 1970
21 Ross A M and Yu P Personal communication (12/4/74)
22 Gallagher J J Oldham H N Wallace A G Peter R H and Kasell J Ventricular aneurysm with ventricular tachycardia Report of a case with epicardial mapping and successful resection Am J Cardiol 35 696 1975
23 Eckberg D L Gault J H Bouchard R L Karliner J S and Ross J Jr Mechanics of left ventricular contraction in chronic severe mitral regurgitation Circulation 47 1252 1973
24 Scampardonis G Yang S S Maranhae V Goldberg H and Gooch A S Left ventricular abnormalities in prolapsed mitral leaflet syndrome Circulation 48 287 1973
25 Gulotta S J Gulco L Padmanabhan V and Miller S The syndrome of systolic click murmur and mitral valve prolapse—A cardiomyopathy? Circulation 49 717 1974
26 Trent J K Adelman A G Wigle E D and Silver M D Morphology of a prolapsed posterior mitral valve leaflet Am Heart J 79 539 1970
27 Barlow J B Bosman C K Pocock W A and Marchand P Late systolic murmurs and non ejection (mid late) systolic clicks An analysis of 90 patients Br Heart J 30 203 1968
28 Read R C and Thal A P Surgical experience with the floppy valve Surgery 59 1673 1966
29 Stannard M Slomen J G Hare W S C and Goble A J Prolapse of the posterior leaflet of the mitral valve A clinical familial and cineangiographic study Br Med J 3 71 1967
30 BonTempo C P Ronan J A de Leon A C and Twigg H L Radiographic appearance of the thorax in systolic click-late systolic murmur syndrome Am J Cardiol 36 27 1975
31 Gooch A S Maranhao V Scampardonis G Cha S D and Yang S S Prolapse of mitral and tricuspid valves in systolic murmur-click syndrome N Engl J Med 387 1218 1972
32 Okada R Galgov S and Leve M Relation of shunt flow and intracardiac pressures to heart valve structure in atrial septal defect Am Heart J 78 781 1969
33 Ranganathan N and Burch G E Gross morphology and arterial supply of the papillary muscle of the left ventricle of man Am Heart J 77 506 1969
34 Armour J A and Randall W C Structural basis for cardiac function Am J Physiol 218 1517 1970
35 Armour J A and Randall W C Electrical and mechanical activity of papillary muscle Am J Physiol 218 1710 1970
36 Armour J A Hageman G R and Randall W C Arrhythmias induced by local cardiac nerve stimulation Am J Physiol 223 1068 1972

cult to distinguish from the aorta[7] Pericardium has also been used to widen the right ventricular outflow tract in Fallot s tetralogy and provided it is not initially redundant has not become aneurismal even in patients with pulmonary artery hypertension[8]

Summary

A surgical method is described which enables a relatively larger aortic prosthetic valve to be inserted. This consists of widening the aortic root with pericardium and inserting the prosthesis slightly obliquely The technique has been successfully applied in all 12 patients on whom it was attempted

Addendum

Since submission of this manuscript for publication a further 10 patients have been subjected to the above procedure with the same gratifying results. The technique has been slightly modified such that sutures are now placed well below the commissure between the left and right coronary cusps into the anterior muscular septum and parietal left ventricular wall In this way the obliquity of valve insertion relative to the plane of the host aortic annulus is further increased Using this additional modification it has not been necessary to insert smaller than a 23 mm Björk Shiley aortic valve even in two children 9 and 10 years of age respectively with rheumatic aortic incompetence

REFERENCES

1 Behrendt D M and Austen W G Current status of prosthetics for heart valve replacement Progr Cardiovasc *Dis* 15 :69 1973
2 Björk V O A new central flow tilting disc valve prosthesis One year s clinical experience with 103 patients, J Thorac Cardiovasc Surg 60 3 1970
3 Konno S Imai, Y Iida Y Nakajima M, and Tatsuno K A new method for prosthetic valve replacement in congenital aortic stenosis associated with hypoplasia of the aortic valve ring J Thorac Cardiovasc Surg 70 909 1975
4 Bernhard W F Poirier V and La Farge C G Relief of congenital obstruction to left ventricular outflow with a ventricular aortic prosthesis, J Thorac Cardiovasc Surg 69 233 19 5
5 McGoon D C Personal communication 19
6 Stenseth J H Danielson G K, and McGoon D C Pericardial patch enlargement of the aortic outflow tract J Thorac Cardiovasc Surg 62 442, 1971
7 Danielson G K. Personal communication 1975
8 Kinsley R. H., McGoon D C., Danielson, G K., Wallace R B and Mair D D Pulmonary arterial hypertension after repair of Tetralogy of Fallot J Thorac Cardiovasc Surg 67 110 1974

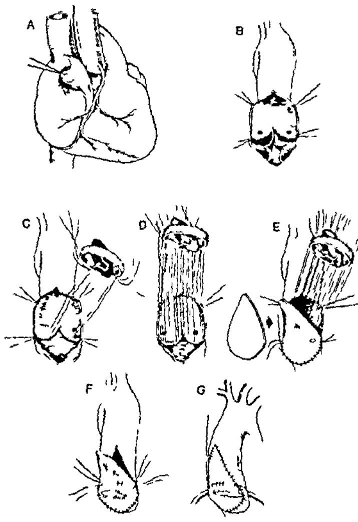


Fig 1 Diagrammatic illustration of the surgical technique *A* Aortotomy *B* Divi ion of aortic annulus *C* and *D* Insertion of sutures in aortic annulus corresponding to regions of attachment of left and right coronary cusps *E* Tear drop shaped pericardial patch sutured to lower one third of aortotomy and its extension across aortic annulus *F* Valve tied in position In region of non coronary sinus valve is sutured to pericardial patch *G* Completion of aortotomy closure with pericardial patch For detailed description see text

nique, a size 21 mm could be inserted Four of the eight were children under the age of 14 years suffering from rheumatic aortic incompetence The other four had rheumatic aortic stenosis, in three of whom there was associated mitral and tricuspid stenosis In the remaining four patients the aortic annulus was not as small but the insertion of a relatively larger Bjork Shiley prosthesis seemed preferable A 23 mm valve was used in three of these and a 25 mm valve in one

Simultaneous aortic and left ventricular pressures were recorded in all instances prior to closure of the thoracotomy and no pressure difference greater than 10 mm Hg was observed None of the patients has shown features of prosthetic valve obstruction or dysfunction The period of follow up ranges from 3 to 12 months

Discussion

The problem of a narrow aortic annulus is encountered by the surgeon under two circumstances Firstly, in the very young in whom it is desirable to insert an adult sized valve to allow for future increase in stroke volume associated with the growth of the patient Secondly, where the pathological process whether congenital or acquired, has resulted in failure of normal development or in fibrous contraction of the aortic annulus The technique described is strongly indicated in such cases but it can be applied to any patient in whom a larger prosthesis relative to the existing annulus, is considered preferable Obstruction to forward flow is obviated by the insertion of a prosthetic valve with an adequately sized ring This is made possible by widening the aortic root with pericardium and by inserting the valve in a slightly oblique plane in relation to the aortic annulus Furthermore, widening of the aortic wall itself will reduce or prevent third orifice obstruction where a ball valve is preferred In patients with subaortic obstruction the method may be combined with resection of muscle or fibrous tissue Although our experience has been confined to the Bjork Shiley valve and we have found a prosthesis one size larger can be used than the annulus would originally have accepted the method is applicable to any design of prosthetic or ring mounted xenograft valve

Other surgical techniques to resolve the problem of a hypoplastic or narrow aortic annulus have been described Konno and associates[1] widened the annulus by dividing the ventricular septum anteriorly and this method has the theoretical advantage of also widening the left ventricular outflow tract However it is a complicated hazardous procedure with considerable risk to the conduction tissue Conduits have been used between the left ventricle and aorta[4, 5] but have all the limitations and uncertainties of a valve containing Dacron tube graft

The possibility of degenerative changes supervening in the pericardial patch seems unlikely Pericardial patches used for the relief of third orifice obstruction in valves with central occluders have not become aneurysmal[6] Indeed in one patient who died traumatically several years postoperatively, the pericardial patch was diffi



Fig 1 Histologic section of the venticular septum from a two-month-old male infant who died of bacterial sepsis Cardiac muscle cells are normal sized and arranged in parallel to each other (Original magnification × 200)



Fig 2 Histologic section of the ventricular septum from a three month-old infant with SIDS Numerous cardiac muscle cells are arranged obliquely and perpendicularly to each other (Original magnification × 250)

of disorganization of cardiac muscle cells was assessed by light microscopy in tissue blocks in which cardiac muscle cells were cut in longitudinal or slightly oblique planes of section

Results

In the 45 hearts of infants with SIDS ventricular septal thicknesses ranged from 5 to 8 mm (mean 6) posterior left ventricular free wall thicknesses ranged from 4 to 7 mm (mean 5) and septal-free wall ratios ranged from 1 0 to 1 5 (mean 1 2) In the 26 control hearts septal and free wall thicknesses ranged from 3 to 8 mm (mean 6) and septal-free wall ratios from 0.9 to 1 2 (mean 1 0) Three of the infants with SIDS (aged 3 5 and 8 weeks) had septal-free wall ratios exceeding 1 3 i e 1 4 1 4 and 1 6 In two of these infants the septum was 7 mm in thickness and in the other infant the septum was 8 mm in thickness

Sudden infant death syndrome (SIDS) Cardiac pathologic observations in infants with SIDS

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Sudden infant death syndrome (SIDS) is the major cause of mortality between one week and one year of age in the United States[1] The primary mechanism responsible for SIDS is unknown, although numerous theories have been proposed[2-5] Recently, a great deal of interest has been directed toward possible cardiac[6, 7] or respiratory[8, 10] mechanisms in SIDS

Asymmetric septal hypertrophy (ASH) is a cardiac disorder characterized by a disproportionately thickened ventricular septum[11, 13] containing numerous bizarrely shaped and disorganized cardiac muscle cells[14, 16] This condition is genetically transmitted as an autosomal dominant trait with a high degree of penetrance,[17] causes sudden and unexpected death in children,[18, 19] and is a recognized cause of cardiac failure and death in infants[20] Therefore, our experience with ASH led us to undertake the present study to determine whether ASH could be implicated as a cause of sudden unexpected death in infancy Hence, in this communication we have described certain morphologic observations made on myocardium from infants who died of SIDS

Materials and methods

Gross anatomic and histological observations were made on the hearts of 45 infants who died of SIDS This study group represented all infants with SIDS who had a necropsy examination at the Office of the Medical Examiner of the State of Maryland between June 1972, and June 1973 In 31 of these 45 patients necropsy examination showed no explanation for death and in 14 patients necropsy findings of focal infection (bronchopneumonia tracheobronchitis, or interstitial pneumonitis) were considered not to be of sufficient magnitude to explain death conclusively In addition, 26 other infants who died suddenly (but not of SIDS) and also had necropsy examination at the Office of the Medical Examiner between June, 1972, and June 1973 served as a control group The cause of death in these infants was trauma congenital heart disease or sepsis Four fetal hearts of 14 to 18 weeks gestation obtained as a result of therapeutic abortions also were analyzed for comparison

The 45 infants with SIDS ranged in age from 2 weeks to 11 months (mean 2 1/2 months) The 26 control infants ranged in age from 4 weeks to 20 months (mean 6 months) Thirty six of the 71 necropsy patients were male and 35 were female 31 patients were white and 40 were black The prevalence of necropsy findings in the SIDS group and in the control group were compared using the two tailed Fisher's exact test

Maximum thicknesses of the ventricular septum and posterior left venticular free wall were measured in each heart Because the specimens used in this study had also been utilized for other investigations, it was not possible to systematically make measurements of the posterobasal left ventricular wall Full thickness blocks were taken from the ventricular septum and left ventricular free wall in transverse planes 1 and 2 cm below the mitral valve anulus as well as from the right ventricular free wall 1 cm below the tricuspid valve anulus Tissue was fixed in 10 per cent formaldehyde processed, embedded in paraffin sectioned at the thickness of 6μ and stained with hematoxylin and eosin The severity and extent

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SIDS resembled those in infants with ASH[10] but were much less marked in severity There was no statistically significant difference between the SIDS and control groups with regard to the prevalence of disorganized cardiac muscle cells The 13 infants with disorganized cells ranged in age from three weeks to 11 months (average four months) and eight of the infants (seven with SIDS and one control) were three months of age or less Cardiac muscle cells in the ventricular septum of the four normal fetuses were virtually all normally arranged

The conducting system was not consistently present in the sections of myocardium studied and, therefore no observations regarding the relation of foci of disorganized cardiac muscle cells to conducting cells were made The pathologic observations in the 45 infants with SIDS are summarized in Fig 4

Discussion

Three hearts from infants with SIDS in this study (two with foci of disorganized cells and one without) showed septal free wall thickness ratios of > 1 3 However the ventricular septal thickness was only 7 mm in two of these infants and 8 mm. in the other In the presence of such small absolute values of septal thickness we cannot be certain that the abnormal ratios are truly indicative of genetically transmitted ASH since very minor errors in wall thickness measurements can result in calculated ratios considerably greater than unity[2] It is also possible that such disproportionate septal thickening may be due to remodeling of the ventricular walls that has been described in early infancy[3] or to right ventricular hypertension[23] that is normally present before birth

Although the disorganized arrangement of cardiac muscle cells present in the ventricular septum of 10 infants with SIDS (as well as in three control infants) resembles that previously described in infants and adults with ASH the morphologic abnormalities in SIDS and ASH differ in two important respects First disorganized cardiac muscle cells in infants with SIDS were normal sized in infants with ASH the disorganized cells are markedly hypertrophied Second the foci of disorganized cardiac muscle cells in SIDS were considerably less marked in severity than is characteristic of ASH

It is perhaps most likely that the foci of disorganized cardiac muscle cells present in the ventricular septum of some infants with SIDS represent normal postnatal remodeling of the arrangement of cardiac muscle cells (these foci were not present in the normal fetal hearts studied) On the other hand we cannot entirely exclude the possibility that these disorganized cells are in some infants an early morphologic manifestation of genetically determined ASH In either case however it is interesting to speculate that abnormally arranged cardiac muscle cells predispose to aberrations of electrophysiologic function and lead to fatal ventricular arrhythmias in certain susceptible infants in whom other environmental stimuli may act as trigger mechanisms.

Summary

To determine the relation between the sudden infant death syndrome (SIDS) and asymmetric septal hypertrophy (ASH) pathologic observations were made in 45 infants who died with SIDS Ventricular septal to left ventricular free wall ratios were normal (< 1.3) in 42 infants and increased in three others (ratios of 1 4 1 4 and 1 6) However in none of these three infants with abnormal septal-free wall ratios was the ventricular septum markedly thickened Small foci of disorganized cardiac muscle cells similar to those observed in patients with ASH (but less marked in severity) were present in the ventricular septum of 22 per cent of the infants with SIDS as well as in 12 per cent of controls Thus we have found little pathologic evidence to suggest that SIDS and ASH are commonly associated although a rare coexistence of these two conditions is possible

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REFERENCES

1 Bergman A B Ray C G Pomeroy M A., Wahl P W., and Beckwith J B Studies of the sudden infant death syndrome in King County Washington. III Epidemiology Pediatrics 49 860 1972.
2. Valdes-Dapena M A Sudden and unexpected death in infancy a review of the world literature Pediatrics 39 123 1967
3 Valdes Dapena M A Progress in sudden infant death research, 1963-1969 in Bergman A B., Beckwith J B



Fig 3 Histologic section of the ventricular septum from an eleven month old infant with SIDS Several bundles of cardiac muscle cells course in a disorganized fashion among more normally arranged bundles of cells. (Original magnification × 75)

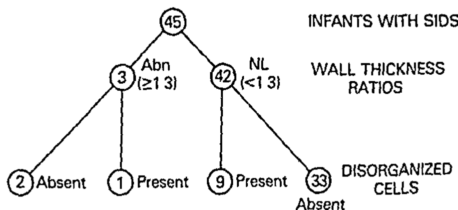


Fig 4 Diagram summarizing the pathologic data in 45 infants with Sudden Infant Death Syndrome (SIDS) *Abn* = abnormal *NL* = normal

Histologic examination showed the cardiac muscle cells in the ventricular septum and left and right ventricular free walls of both control and SIDS hearts to be normal sized (transverse cell diameters 5 to 15μ) The vast majority of cardiac muscle cells in the ventricular septum and virtually all cells in the ventricular free walls were normally arranged (i e, in parallel alignment) (Fig 1) However, small foci of cardiac muscle cells in which adjacent cells were arranged obliquely and perpendicularly to each other (Fig 2) were present in the ventricular septum of 13 infants, including 10 (22 per cent) of the 45 infants with SIDS and three (12 per cent) of the 26 infants in the control group These foci were often near the junction of ventricular septum with left and right ventricular free walls and involved from 10 to 50 cardiac muscle cells no more than three foci were present in any one section of myocardium In addition, ventricular septal myocardium from two of the 10 infants with SIDS (having foci of disorganized cells in the septum) also showed small areas in which groups or bundles of cardiac muscle cells coursed in various directions among more normally arranged bundles of cells [8, 21] (Fig 3) Foci of disorganized cardiac muscle cells however were not observed in areas of myocardium where adjacent muscle bundles came together Disorganized cardiac muscle cells observed in the ventricular septum of infants with

Double ventricular parasystole Intermittency and its relation to re entrant premature beats

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Several cases of intermittent parasystole have been studied to demonstrate the mechanism of protection of the parasystolic focus

Presently it is thought that intermittent parasystole occurs as a result of temporary loss of entrance block It has been observed that parasystolic centers appear to be protected from sinus beats and other ventricular ectopic impulses both early and late in their cycles Thus phase 3 and phase 4 blocks in the surrounding fibers of the focus have been proposed as a possible explanation for intermittency

The present case of double ventricular parasystole offers a unique opportunity to elucidate the mechanism of intermittent parasystole and its relation to re entrant premature beats

Report of electrocardiogram

Fig 1 shows a continuous Lead V electrocardiogram (ECG) taken from a 49 year old man with a history of anterolateral myocardial infarction The basic sinus rhythm is frequently interrupted by premature systoles exhibiting two distinct types of QRS configurations The small bizarre QRS configuration of beats 3 8 11 14 18 20 21 23 26 28 and 31 is designated as XA beats 2 4 9 16 22 and 24 are designated as XB The coupling intervals of XB premature systoles show wide variation measuring between 0 86 and 1 20 sec The shortest interectopic interval measures 2 00 and 2 08 sec (between beats 2 and 4 and 22 and 24) with the longer interectopic intervals (between beats 4 and 9 and 9 and 16 and 16 and 22) being multiples thereof (i e 2 00 × 3 2 00 × 3 and 1.92 × 3 sec respectively) Thus XB premature systoles could represent ventricular parasystole

In contrast the bizarre QRS complex of XA shows coupling intervals varying from 0 56 to 1 06 sec Of these XA premature systoles beats 18 20 21 and 23 seem to emerge in a series yet their interectopic intervals are uneven (1 74 1 58 and 1 78 sec) Furthermore the longer interectopic intervals do not correspond to simple multiples of any of the basic intervals (with the exception of the intervals between beats 8 and 11 and 14 and 18 both measuring 3 16 sec or 1 58 sec × 2) Therefore simple ventricular parasystole does not appear to explain these beats Beats 3 and 8 appear with an interectopic interval of 5 70 sec If one assumes that this interval represents either 3 or 4 parasystolic cycles then the cycle length must be 1 90 or 1 43 sec respectively Neither of these intervals coincides with the previous cycle length of 1.58 sec however and they appear to be either too long or too short But measurement of the interval from beat 4 to beat 8 is exactly three times the shortest interval (4 74 sec = 1 58 sec × 3) This relationship may suggest that the parasystolic pacemaker was discharged and its timing reset by beat 4 Similarly beats 12 24 and 29 must also have penetrated into the ectopic focus and reset it as shown by open circles In the diagram which is a modification of the one used by Cohen and associates[3] the horizontal stippled bars represent protection of the XA and XB parasystolic foci and the blank spaces in between indicate temporary loss of the protective entrance block Thus the XA premature systoles have the characteristics of an intermittent type of parasystole

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and Ray C G editors Sudden infant death syndrome Proceeding of the Second International Conference on Causes of Sudden Death in Infants Seattle and London 1970 University of Washington Press p 3
4 Marx J L Crib death Some promising leads but no solution yet Science **189** 367 1975
5 Valdes Dapena M A Sudden unexpected and unexplained death in infancy—a status report—1973 N Engl J Med **289** 1195 1973
6 Salk L Grellong B A and Dietrich J Sudden infant death Normal cardiac habituation and poor autonomic control N Engl J Med **291** 219 1974
7 James T N Sudden death in babies new observations in the heart Am J Cardiol **22** 479 1968
8 Naeye R L Pulmonary arterial abnormalities in the sudden infant death syndrome N Engl J Med **289** 1167 1973
9 Naeye R L Hypoxemia and the sudden infant death syndrome Science **186** 837 1974
10 Steinschneider A Prolonged apnea and the sudden infant death syndrome clinical and laboratory observations Pediatrics **50** 646 1972
11 Henry W L Clark C E and Epstein S E Asymmetric septal hypertrophy echocardiographic identification of the pathognomonic anatomic abnormality of IHSS Circulation **47** 225 1973
12 Epstein S E Henry W L Clark C E Roberts W C Maron B J Ferrans V J Redwood D R and Morrow A G Asymmetric septal hypertrophy Ann Intern Med **81** 650 1974
13 Roberts W C Valvular subvalvular and supravalvular aortic stenosis Morphologic features Cardiovasc Clin **5** 104 1973
14 Ferrans V J Morrow A G and Roberts W C Myocardial ultrastructure in idiopathic hypertrophic subaortic stenosis A study of operatively excised left ventricular outflow tract muscle in 14 patients Circulation **45** 769 1972
15 Maron B J Ferrans V J Henry W L Clark C E Redwood D R Roberts W C Morrow A G and Epstein S E Differences in distribution of myocardial abnormalities in patients with obstructive and nonobstructive asymmetric septal hypertrophy (ASH) Light and electron microscopic findings Circulation **50** 436 1974
16 Teare D Asymmetrical hypertrophy of the heart in young adults Br Heart J **20** 1 1958
17 Clark C E Henry W L and Epstein S E Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis N Engl J Med **289** 709 1973
18 Maron B J Henry W L Clark C E Redwood D R Roberts W C and Epstein S E Asymmetric septal hypertrophy in childhood Circulation **53** 9 1976
19 Frank S and Braunwald E Idiopathic hypertrophic subaortic stenosis Clinical analysis of 126 patients with emphasis on the natural history Circulation **37** 759 1968
20 Maron B J Edwards J E Henry W L Clark C E Bingle G J and Epstein S E Asymmetric septal hypertrophy (ASH) in infancy Circulation **50** 809 1974
21 Maron B J Edwards J E Ferrans V J Clark C E Lebowitz E A Henry W L and Epstein S E Congenital heart malformations associated with disproportionate ventricular septal thickening Circulation **52** 926 1975
22 Larter W E Allen H D Sahn D J and Goldberg S J The asymmetrically hypertrophied septum Further differentiation of its causes Circulation **53** 19 1976
23 Goodman D J Harrison D C and Popp R L Echocardiographic features of primary pulmonary hypertension Am J Cardiol **33** 438 1974

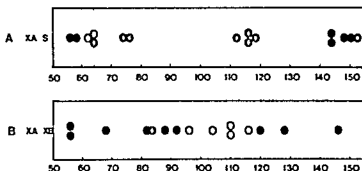


Fig 2 Diagrammatic illustrations of the interval between each of the conducted XA beats and the following sinus (*A*) or XB (*B*) beat. Closed circles represent the beats which do not disturb the XA parasystolic cycle and double circles represent the beats which cause prolongation of the next parasystolic cycle. Note the different ranges of open circles indicating failure of protection of the focus in A and B. See text for discussion

tissue refractory because of this concealment resulting in delayed conduction and a longer interectopic interval. One might argue that because the interval between beats 26 and 28 is quite long (2.08 sec) this explanation would be unlikely even in the presence of exit delay from the parasystolic focus. An alternative explanation could be that beat 27 initiates re entry in the fibers around the XA focus which are partially depolarized by phase 4 of the previous XA beat 26 and thus the next beat (beat 28) is actually a re entrant premature beat from this previous depolarization of beat 27

This possibility is further illustrated in Fig 3*A* and 3*B*. Fig 3*A* represents the different QRS configurations of sinus XA and XB beats. XA and XB beats have QRS axis shifted more leftward than the sinus beat suggesting that these ectopic impulses most likely originate in the area close to the left posterior fascicle and the right bundle branch and exhibit delayed conduction in the left anterior fascicle. Fig 3*B* shows XA parasystolic rhythm and coupled premature systoles with varying degrees of fascicular block and progressive prolongation of coupling intervals (0.46 0.50 0.54 and 0.58 sec). Beat 2 has the same QRS configuration as XA but the S wave in Lead I suggests the concomitant delay in the right bundle branch. Beats 6 and 8 seem to represent left posterior hemiblock and left posterior hemiblock with right bundle branch block respectively. Beat 4 has an intermediate configuration of beats 2 and 6 probably indicating left bundle branch block pattern. From these findings one can assume that these coupled premature systoles are re entrant beats initiated by each preceding XA beat. Close resemblance between the XA beat and beat 2 further suggest that re entry occurs within or in the immediate vicinity of the XA focus. But these re-entrant beats do not appear to penetrate into the XA focus in a retrograde fashion as evidenced by relatively constant XA cycle. Progressive changes in the coupling interval and the QRS configuration would be explained in terms of a combination of factors particularly the change in conduction time within the re entrant pathway progressive delay in the left posterior fascicle and right bundle branch due to their refractoriness and delay in the left anterior fascicle due to an anatomical location of the XA focus

Discussion

El Sherif and Samet demonstrated the presence of multiple ventricular parasystolic activity and a few cases of double ventricular parasystole have been reported in literature[3, 4]

The present case demonstrates double parasystolic foci (one focus manifesting complete protection and the other focus manifesting intermittent parasystole) and provides us with some insight into the mechanism of intermittency. According to the observations in Fig 2 both short and long XA to sinus and XA to XB intervals permit continuation of XA parasystolic cycle but the range of dissipation of protection by the sinus beats is quite narrow (Fig 2*A*) and in contrast much wider when the XA focus is challenged by XB beats (Fig 2*B*). Therefore the intermittent parasystolic focus in this case must be surrounded by two types of fibers with different degrees of refractoriness and diastolic depolarization which play a role in protecting the focus from other impulses. The fibers located between the

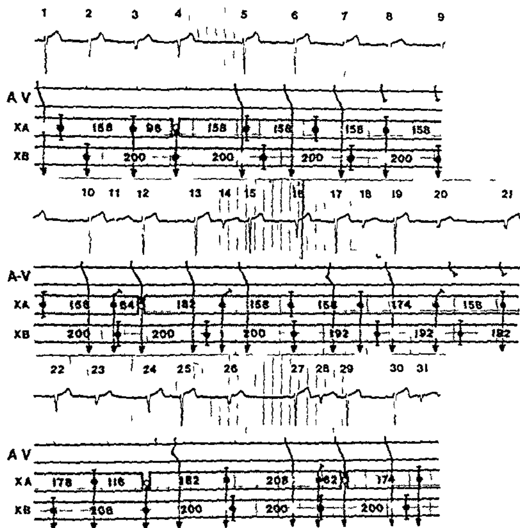


Fig 1 Consecutive records of V with diagrams of the proposed mechanism Time intervals are expressed in hundredths of a second in this and subsequent illustrations *A V* atrioventricular conduction *XA* one parasystolic discharge which is considered to be intermittent *XB* second parasystolic discharge Beats 17 and 25 have apparent short PQ intervals and appear to be supraventricular premature beats See text for discussion

In Fig 2 all the intervals between each of the conducted XA beats and the following sinus (S) or XB beat are plotted on the horizontal axis Data were obtained from several strips recorded on the same day Closed circles represent the beats which did not disturb the XA parasystolic cycle It is clearly demonstrated that the XA focus is protected from the sinus and XB beats in both the early and the late phases of the parasystolic cycle It is seen in Fig 2*A* that the sinus impulses with coupling intervals of 0 62 and 0 64 sec (open circles beats 29 and 12) penetrate into the XA focus and cause discharge and resetting of the focus Fig 2*B* also shows this relationship but the range of open circles (0 96 to 1 16 seconds) in which the XA parasystolic cycle is interrupted by XB beats is later in the cycle and wider than that shown in Fig 2*A* Furthermore Fig 1 and 2 indicate that if a sinus or supraventricular beat (beats 13 25 and 30, represented by double circles in Fig 2) falls within a certain period following a penetrating beat the next parasystolic cycle appears to be prolonged (1 82 1 82 and 1 74 sec respectively) The same feature is found between two consecutive XB beats (e g beats 18 and 20 21 and 23 and 26 and 28) which contain a sinus beat or XB beat However there is no correlation observed between the timing of these penetrating extraneous impulses relative to the XA beat and the degree of prolongation of the XA cycle Whenever the conducted sinus beats fall within 0 64 to 1 52 sec after either a preceding conducted XA beat (beats 18 and 26) or a sinus or XB beat which discharged the XA focus (beats 12 29 and 24) then these sinus beats are probably blocked in the region surrounding the XA focus and never discharge the focus Instead they may partially penetrate into this region in a concealed fashion Thus the next predicted XA beat from the regular automatic focus may find the surrounding

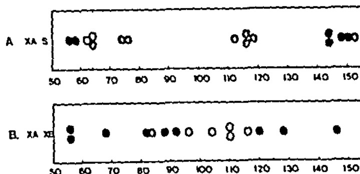


Fig 2 Diagrammatic illustrations of the interval between each of the conducted XA beats and the following sinus (A) or XB (B) beat. Closed circles represent the beats which do not disturb the XA parasystolic cycle and double circles represent the beats which cause prolongation of the next parasystolic cycle. Note the different ranges of open circles indicating failure of protection of the focus in A and B. See text for discussion

tissue refractory because of this concealment resulting in delayed conduction and a longer interectopic interval One might argue that because the interval between beats 26 and 28 is quite long (2 08 sec) this explanation would be unlikely even in the presence of exit delay from the parasystolic focus An alternative explanation could be that beat 27 initiates re entry in the fibers around the XA focus which are partially depolarized by phase 4 of the previous XA beat 26 a d thus the next beat (beat 28) is actually a re entrant premature beat from this previous depo larization of beat 27

This possibility is further illustrated in Fig 3A and 3B Fig 3A represents the different QRS configurations of sinus XA and XB beats XA and XB beats have QRS axis shifted more left ward than the sinus beat suggesting that these ectopic impulses most likely originate in the area close to the left posterior fascicle and the right bundle branch and exhibit delayed conduction in the left anterior fascicle Fig 3B shows XA parasystolic rhythm and coupled premature systoles with varying degrees of fascicular block and progressive prolongation of coupling intervals (0 46 0 50 0 54 and 0 58 sec) Beat 2 has the same QRS configuration as XA but the S wave in Lead I suggests the concomitant delay in the right bundle branch Beats 6 and 8 seem to represent left posterior hemiblock and left posterior hemi block with right bundle branch block respective ly Beat 4 has an intermediate configuration of beats 2 and 6 probably indicating left bundle branch block pattern From these findings one can assume that these coupled premature systoles are re entrant beats initiated by each preceding XA beat Close resemblance between the XA beat and beat 2 further suggest that re entry occurs within or in the immediate vicinity of the XA focus But these re-entrant beats do not appear to penetrate into the XA focus in a retrograde fashion as evidenced by relatively constant XA cycle Progressive changes in the coupling interval and the QRS configuration would be explained in terms of a combination of factors particularly the change in conduction time within the re entrant pathway progressive delay in the left posterior fascicle and right bundle branch due to their refractoriness and delay in the left anterior fascicle due to an anatomical location of the XA focus

Discussion

El Sherif and Samet demonstrated the presence of multiple ventricular parasystolic activity and a few cases of double ventricular parasystole have been reported in literature

The present case demonstrates double parasys tolic foci (one focus manifesting complete protec tion and the other focus manifesting intermittent parasystole) and provides us with some insight into the mechanism of intermittency According to the observations in Fig 2 both short and long XA to sinus and XA to XB intervals permit continuation of XA parasystolic cycle but the range of dissipation of protection by the sinus beats is quite narrow (Fig 2A) and in contrast much wider when the XA focus is challenged by XB beats (Fig 2B) Therefore the intermittent parasystolic focus in this case must be surrounded by two types of fibers with different degrees of refractoriness and diastolic depolariza tion which play a role in protecting the focus from other impulses The fibers located between the

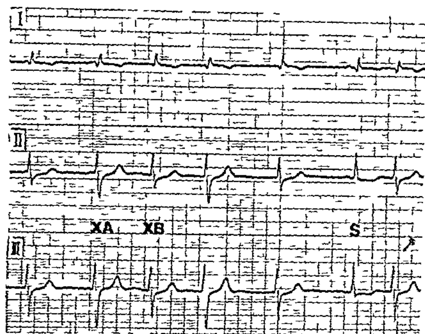


Fig 3A Simultaneous records of Leads I II and III showing different configurations of QRS of sinus (S) and XA and XB beats

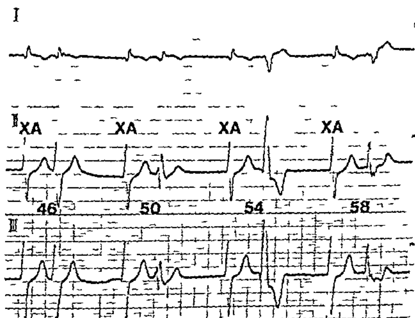


Fig 3B Re entrant bigeminy coupled with XA parasystolic rhythm See text for discussion

major fascicles and the XA focus may have a shorter refractory period and less steep diastolic phase 4 depolarization than those between the XA and XB foci These findings have never been documented before although Cohen and associates[3] reported a case of intermittent parasystole which had both early and late phases of protection due to its own refractoriness and diastolic depolarization in the focus or in the tissues surrounding it In their study, the zone of susceptibility between these two phases of protection was limited to a short time interval early in diastole Also, in a case of double ventricular parasystole, recently reported by Hiejima and Poh[5] one focus was depolarized by the other parasystolic beat only at its supernormal period

It could be postulated that during the early phase of diastolic depolarization in the fibers around the parasystolic focus concealed conduction of sinus beats into these areas evokes exit delay of the parasystolic impulse resulting in prolongation of the next parasystolic cycle Singer and associates[4] have proposed an alternate explanation for an irregularity in the parasystolic cycle In their case manifest re entry resulted in

premature beats coupled to the parasystolic beats and concealed re entry could produce prolongation of the parasystolic cycle

In the presence of various degrees of refractoriness and exit delay in the fibers around the parasystolic focus a re entry movement can be predicted in this area Re entrant bigeminy coupled to the parasystolic beats as shown in Fig 3B may support such a possibility

Re entry within the parasystolic focus can also be induced by sinus beats giving rise to a pattern of bigeminy Schamroth and Marriott[10] described two cases which showed alternate extrasystolic and parasystolic impulse formation from the same ectopic focus Their explanation was that the extrasystole was produced by impulses falling in the supernormal period The present observations and the study of Singer and associates however demonstrate the possibility of re entry within the focus or the fibers around the focus as a mechanism of coupled premature systole Thus our case may represent a link between re entry and automaticity

Summary

Critical analysis of a case of double ventricular parasystole revealed that one parasystolic focus manifested complete protection whereas the second focus appeared to be intermittent protected from sinus and other impulse formation both early as well as late in the parasystolic cycle The zone of protection failure during which extrinsic impulses could penetrate into the parasystolic focus and discharge it is observed between these early and late phases of protection When the intermittent parasystolic focus is challenged by the other parasystolic beat this zone is much wider and is located later in the cycle than the sinus beat

According to this observation it is supposed that the intermittent parasystolic focus in this case is anatomically surrounded by two types of fibers each showing different degrees of phase 3 and phase 4 block The fibers located between the major fascicles and the intermittent parasystolic focus may have a shorter phase 3 and a less steep phase 4 depolarization than those located between two parasystolic foci It is also demonstrated that during the phase 4 depolarization in these fibers around the focus concealed conduction into this area by the sinus beat evoked exit delay of the parasystolic impulse resulting in prolongation of the next parasystolic cycle In this situation a re entry movement around the focus was predicted and as expected a re entrant bigeminy coupled with the parasystolic rhythm was observed

REFERENCES

1 Watanabe Y Reassessment of parasystole Am Heart J 81 451 1971
2 Steffens T G Intermittent ventricular parasystole due to entrance block failure Circulation 44 442, 1971
3 Cohen H Langendorf R, and Pick A Intermittent parasystole—mechanism of protection Circulation 48 61 1973
4 Kinoshita S and Tanabe Y Second degree entrance block in intermittent ventricular parasystole Chest 67 236 1975
5 Hiejima K and Toh T D Double ventricular parasystole Supernormal phase of conduction as a mechanism of intermittent parasystole Report of a case Circulation 53 572 1976
6 El Sherif N and Samet P Multiform ventricular ectopic rhythm Evidence for multiple parasystolic activity Circulation 51 492, 1975
7 Chung K Y Walsh T J and Massie E Double ventricular parasystole Am Heart J 67 162, 1964
8 Roelandt J Pool J and Schamroth L Double bifocal ventricular parasystole J Electrocardiol 5 86 1972
9 Singer D H, Parameswaran R Drake F T Meyers, S N and DeBoer A A Ventricular parasystole and re-entry Clinical electrophysiological correlations Am Heart J 88 9 1974
10 Schamroth, L and Marriott H J L Intermittent ventricular parasystole with observations on its relationship to extrasystolic bigeminy Am J Cardiol 7 799 1961

Mitral valve prolapse with atrioventricular and sinoatrial node abnormalities of long duration

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The syndrome of mid late systolic murmur and non ejection click with mitral valve prolapse is frequently associated with atrial and ventricular arrhythmias[1, 3] and with sudden death[3, 6, 7] The relationship between the occurrence of sudden death and arrhythmias is, however unclear Although atrioventricular block (AVB) is not widely appreciated as a part of this syndrome and is not mentioned in several large patient series,[2, 3, 5] several cases of AVB associated with mitral valve prolapse have been reported[1, 4, 8, 10] Two patients described by Gulotta[1] had perma nent pacemakers implanted because of recurrent syncopal episodes which appeared related to the development of complete AVB in one of these patients, although the etiology of syncope could not be documented in the other The subsequent clinical course of these patients as well as of the others described with AVB is however, not reported The occurrence of sinus bradycardia is also described in a small number of patients with this syndrome[1, 11] and the course of these patients is similarly unknown

The patient described in this report is a 20-year old male with documented mitral valve prolapse sinus bradycardia with marked sinus arrhythmia, and high grade AVB of many years duration, probably with onset in infancy Long term follow up in this patient demonstrated no significant changes in cardiac rhythm to the present time Of interest is the documented lack of relationship of symptoms of lightheadedness and near syncope to any rhythm disturbances

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Case report

G B is a 20 year old white male admitted to the New England Deaconess Hospital for evaluation of severe chest pains and episodes of severe lightheadedness and transient syncope He was first noted to have an electrocardiographic abnormality sometime during the first year of life and at the age of two years a heart murmur was detected At age eight he was admitted to another hospital with complaints of fatigue and mild shortness of breath following exercise and vague sharp pains across the lower anterior chest unrelated to activity At that time cardiac examination was unremarkable except for a Grade II III/VI blowing systolic murmur heard along the lower left sternal border and varying intensity of the first heart sound Electrocardiograms demonstrated AVB varying between first degree second degree of the Wenckebach type and complete AVB Chest x ray was normal Cardiac catheterization was performed at that time and demonstrated normal right heart pressures normal cardiac output and no evidence of intracardiac shunting He was discharged without treatment and without restriction of activity

There was little change in symptoms until six months prior to admission when he began to experience up to three to four episodes of retrosternal pain per day lasting from 30 seconds to several minutes Pain appeared to be unrelated to exertion emotional stress position or food intake and was usually associated with a sensation of lightheadedness and occasional brief episodes of syncope or near syncope which he denied ever occurred in the absence of pain At that time he was again admitted to another hospital for evaluation Electrocardiographic findings were unchanged from those of his earlier hospitalization With treadmill exercise testing the sinus rate increased to 189 beats per minute with only first degree AVB Precordial pain occurred during exercise testing but was not accompanied by any ST segment changes Cardiac catheterization was repeated with findings of a pulmonary arterial pressure of 28/12 mm Hg and a pulmonary capillary wedge mean pressure of 12 mm Hg with a V wave of 22 mm Left ventriculography showed normal contractility with slight prolapse of the posterior leaflet of the mitral valve and minimal mitral regurgitation Electrophysiological studies demonstrated an increased A H interval of 190 msec with a normal H Q interval of 55 msec With atrial pacing at a rate of 63 per minute further A H prolongation was observed with development of second degree AVB of the Wenckebach type and only minimal H Q prolongation to 60 msec Administra

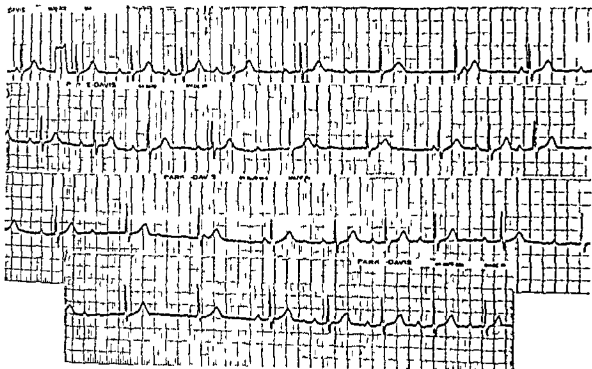


Fig 1 Continuous Lead II rhythm strip showing marked sinus arrhythmia with first-degree atrioventricular block and periods of second-degree block of the Wenckebach type long pauses terminated by junctional escape beats at a rate of 4 minute

tion of atropine resulted in an atrial rate of 100 per minute with complete AVB the H Q interval remaining at 60 msec

Following discharge he continued to experience a further increase in severity of chest pains and was admitted to the New England Deaconess Hospital Physical examination revealed a well-developed young man in apparent good health with no stigmata of Marfan's syndrome Blood pressure was 1?0 2 Carotid pulses and jugular venous pulsations were normal The chest was clear There were no abnormal cardiac impulses. The first and second heart sounds were normal with no audible third or fourth heart sounds A midsystolic click was heard at the cardiac apex and a Grade II/VI mid to-late systolic murmur was audible along the left sternal border and at the cardiac apex with radiation toward the left axilla and increased slightly during a valsalva maneuver and in the upright position Examination was otherwise within normal limits. A typical rhythm strip is shown in Fig 1 Telemetry monitoring showed marked variations in sinus rate ranging from 30 to 80 per minute AVB varied between first degree second degree of the Wenckebach type and 2 1 or greater block with appearance of a junctional escape rhythm at rates varying between 30 to 43 per minute occasionally as low as 20 per minute during sleep Electrocardiograms otherwise were within normal limits (Fig 2)

During hospitalization he continued to have episodes of chest pain and lightheadedness which were not associated with any change in cardiac rate or rhythm or in blood pressure Furthermore the lowest heart rates observed were not associated with any symptoms. Chest pains were not affected by nitroglycerin or by propranolol at a dose of 40 mg per day Although the latter did not affect the cardiac rhythm it was decided not to further increase the dose because of the period of marked bradycardia. Because of the possibility of his symptoms being hypoglycemia related a glucose tolerance test was performed which showed a three-hour blood sugar of less than 40 mg per cent although no symptoms occurred during the test and his spontaneously occurring symptoms did not respond to the diet designed to avoid hypoglycemia Four months later because of persistent pain coronary angiography was performed at another hospital and revealed normal coronary arteries

His medical history was otherwise negative except for premature birth (birth weight of 3 lbs 6 ozs.) to an Rh negative mother with development of postnatal jaundice treated with exchange transfusions. Family history was remarkable in that his father died at age 41 having undergone surgery for aortic valvular disease of unknown type and a brother has an undefined heart murmur

Discussion

Atrioventricular block (AVB) appears to be uncommonly associated with mitral valve prolapse Review of the literature reveals nine cases of reported first degree AVB alone three cases of second degree AVB and two cases of complete AVB associated with this syndrome From a series of 26 patients with mitral prolapse Gulotta and associates have described four who did demonstrate AVB One of these patients had experienced several syncopal episodes and although His bundle studies were normal this

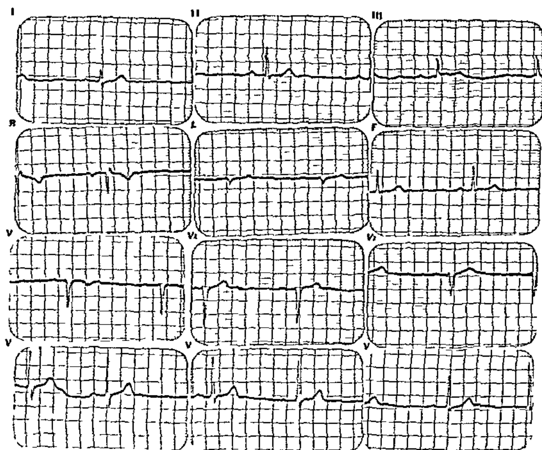


Fig 2 Twelve lead electrocardiogram which is normal except for sinus bradycardia with sinus arrhythmia and first degree atrioventricular block

patient soon after study developed right bundle branch block second degree AVB and progression to complete AVB with occurrence of syncope Another patient was demonstrated to have intermittent second degree AVB proximal to the bundle of His and experienced recurrent syncopal episodes the etiology of which could not be documented Both of these patients had permanent pacemakers inserted but their subsequent course is not described The site of AVB in the other patients reported is not known However the occasional reports of right and left bundle branch blocks and left anterior fascicular block in association with mitral prolapse[1] would indicate conduction system disease distal to the bundle of His Involvement of the sinoatrial node is also described in an occasional patient with sinus bradycardia periods of sinus arrest, and exaggerated sinus arrhythmia[1] The long term follow up of none of these patients is described That the underlying process resulting in myxomatous changes in the mitral valve or in abnormal left ventricular contractility may involve the cardiac conduction system seems a possibility although this has not been demonstrated Shappell and colleagues[6] have reported a patient with mitral prolapse QT interval prolongation and sudden death in whom the conduction system was studied in detail pathologically with no detectable abnormalities Sudden death is recognized to be associated with this syndrome[3] and it is conjectural at present whether this may be related to conduction system disease It is perhaps more likely that the sudden death is attributable to the ventricular tachyarrhythmias which frequently occur[1 3]

The 20 year old patient with mitral prolapse and minimal mitral regurgitation described in the present report demonstrated intermittent marked sinus bradycardia and sinus arrhythmia periods of very slow junctional escape rate and AVB varying from first degree to high grade Electrophysiologic studies demonstrated the site of AVB to be proximal to the bundle of His The onset of the murmur and AVB at an early age in this patient suggest a congenital etiology Unlike other reports in the literature long term follow up is available for this patient with documented persistence of the conduction abnormality for at least 12 years and most likely from the first year of life without apparent change Furthermore this patient s symptoms of chest pain and severe

lightheadedness and near syncope were documented to bear no relationship to his cardiac rhythm and remain unexplained. Because of this and the stability of his course, it was decided that cardiac pacing was probably not warranted at the present time. It is suggested that such rhythm disturbances may not show progression or may progress at a very slow rate, and that etiologies other than severe bradycardia should be considered for symptoms of lightheadedness and syncope in this setting.

Summary

A 20-year-old patient with mitral valve prolapse and minimal mitral regurgitation associated with intermittent marked sinus bradycardia and sinus arrhythmia, periods of very slow junctional escape rhythm, and atrioventricular block proximal to the bundle of His varying from first-degree to high grade is described. Both the murmur and the atrioventricular block has been documented since the age of eight years and probably since the first year of life and has shown no subsequent progression. The patient's symptoms of chest pain and severe lightheadedness and near syncope have been shown by telemetry electrocardiographic monitoring to be unrelated to changes in cardiac rhythm.

REFERENCES

1. Gulotta S J, Gulco L, Padmanabhan V, and Miller S: The syndrome of systolic click, murmur and mitral valve prolapse—a cardiomyopathy? Circulation 49:717, 1974.
2. Cooch A, Vicencio E, Maranhao V, and Goldberg H: Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome. Am J Cardiol 29:611, 1972.
3. Hancock, E W, and Cohn K: The syndrome associated with mid-systolic click and late systolic murmur. Am J Med 41:183, 1966.
4. Pocock W A, and Barlow J B: Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome. Am J Med 51:731, 1971.
5. Jeresaty R M: The syndrome associated with mid-systolic click and/or late systolic murmur. Chest 59:643, 1971.
6. Shappell S D, Marshall C E, Brown R E, and Bruce T A: Sudden death and the familial occurrence of mid-systolic click, late systolic murmur syndrome. Circulation 48:1128, 1973.
7. Shell W E, Walton J A, Clifford M E, and Willis P W: The familial occurrence of the syndrome of mid-late systolic click and late systolic murmur. Circulation 39:327, 1969.
8. Barlow J B, Bosman C K, Pocock W A, and Marchand P: Late systolic murmurs and non-ejection ("mid-late") systolic clicks. Br Heart J 30:203, 1968.
9. Barlow J B, Marchand P, Pocock W A, and Denny M: The significance of late systolic murmurs. Am Heart J 66:443, 1963.
10. Schall S F, Fontana M E, Wooley C F: Mitral valve prolapse syndrome—spectrum of conduction defects and arrhythmias. Circulation 50(Suppl 3):9, 1974.
11. DeMaria A N, Amsterdam E A, Vismara L A, et al: The variable spectrum of rhythm disturbances in the mitral valve prolapse syndrome. Circulation 50(Suppl 3):27, 1974.
12. Leon D F, Leonard J J, Kroetz, F W, et al: Late systolic murmurs, clicks and whoops arising from the mitral valve. Am Heart J 72:325, 1966.

Clinical pathologic conference

Purulent pericarditis with asymmetric cardiac tamponade A cause of death months after coronary artery bypass surgery

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Clinical history

The patient was a 39 year old white man with a history of polycystic kidney disease atherosclerotic coronary artery disease and recent coronary artery bypass graft surgery

He had been generally well until 24 years of age when hypertension was noted and the diagnosis of bilateral polycystic kidneys was made Over the ensuing 15 years he developed slowly progressive renal failure and by age 38 he required chronic renal dialysis At age 33 he also developed angina pectoris which became progressively incapacitating Cardiac catheterization performed 16 months before death showed severe three vessel coronary artery disease Due to Class IV angina pectoris unresponsive to maximal medical therapy he had saphenous vein coronary artery bypass grafts placed in his left anterior descending and left circumflex coronary arteries 6 months before death His postoperative course was initially complicated by mediastinitis and wound dehiscence but subsequently he did well and was discharged from the hospital markedly improved with regard to his angina He continued to undergo renal hemodialysis and was apparently well until 2 days before his final admission when he developed fever nausea and vomiting and lower chest and upper abdominal pain which brought him to the hospital The patient was not a smoker and had normal serum cholesterol but elevated triglycerides His family history was positive for polycystic kidney disease and systemic hypertension but negative for coronary artery disease

Physical examination on admission showed a pulse of 140 per minute respirations 36 per minute blood pressure 140/90 mm Hg and temperature 39 3° C Pertinent findings included no neck vein distention bilateral axillary adenopathy, a still healing median sternotomy and clear lungs bilaterally He had a palpable apex beat at the fifth intercostal space midclavicular line clear heart sounds and no rub murmur or gallop His liver edge was felt 6 cm below the right costal margin and was nonpulsatile There was no peripheral edema cyanosis or clubbing Laboratory values on admission included a hematocrit of 28 per cent hemoglobin 8 9 Gm per 100 ml and white blood count of 8,700 per cubic millimeter with a normal differential Urinalysis showed 5 to 10 white blood cells per high power field and no glucose acetone or bacteria Serum electrolytes were normal serum urea nitrogen was 72 mg per 100 ml and creatinine was 14 mg per 100 ml Serum creatinine phosphokinase was 18 amylase 46 fasting triglycerides 322 cholesterol 225 mg per 100 ml His chest x ray was essentially unchanged from one taken 4 months earlier on discharge from the hospital and showed mild cardiomegaly An electrocardiogram (ECG) (Fig 1) showed small q s in Leads II III qV_F and nonspecific ST T wave changes also

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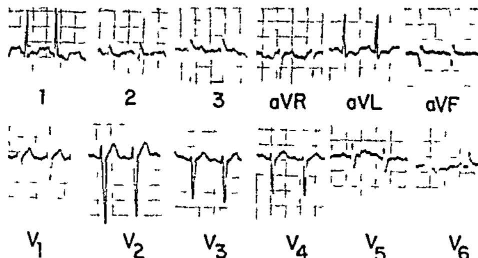


Fig 1 ECGs taken 2 days before death showing evidence of remote inferior myocardial infarction The ECG showed no significant change from one taken shortly after operation

unchanged from one taken on hospital discharge

Hospital course

Over the first 12 hours after admission he remained febrile to 40 7° C and his blood pressure gradually fell to 100/70 mm Hg Numerous cultures were obtained and methicillin and gentamycin therapy started An echocardiogram (Fig 2) showed a sizeable echo free space posterior to the heart but none anteriorly A Swan Ganz catheter was placed Mean right atrial pressure was 25 mm Hg right ventricular pressure 40/25 pulmonary artery 40/25 and pulmonary artery wedge 25/30 Radial artery pressure at that time was 80/60 (Fig 3) Shortly thereafter he sustained a cardiopulmonary arrest and could not be resuscitated

Clinical discussion

Dr J O'Neal Humphries There are three important features of the acute distress which developed in the last 2 days of life of this man with chronic renal disease hypertension and severe coronary artery disease First he had severe unrelenting lower chest and upper abdominal pain second he was afebrile and third he presented signs and symptoms of cardiorespiratory distress leading in 2 days to shock and death

An acute myocardial infarction must certainly be considered in this total setting but the constant pain for the entire 2 days would be

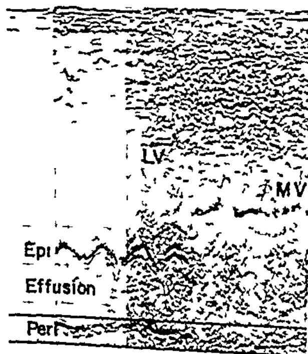


Fig 2 Unretouched echocardiogram taken hours before death showing a large sonolucent space posteriorly which represented a large loculated pericardial effusion There was no evidence of effusion anteriorly LV Left ventricular cavity MV mitral valve Epi epicardial peri pericardium

atypical The absence of any change of the ECG also ruled against this possibility The same arguments would apply to the possibility of pulmonary embolus There was no evidence of pneumothorax or ruptured esophagus Although dissecting hematoma of the aorta in a chronically

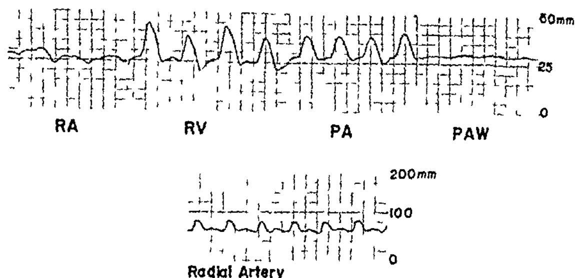


Fig 3 Swan Ganz pressure tracings from the right heart performed shortly before death showing elevation and equalization of right atrial (RA) right ventricular (RV) and pulmonary arterial (PA) diastolic and pulmonary arterial wedge pressures (PAW) Simultaneous radial arterial pressure tracing is also shown

hypertensive man cannot easily be excluded, the pain was atypical for this there were no alterations in the peripheral pulses and the mediastinal silhouette on the chest radiograph was unchanged Dysfunction of a subdiaphragmatic organ must be considered as a cause for the pain on presentation The absence of tenderness of the liver made a distended liver capsule unlikely Normal bowel sounds and the absence of abdominal tenderness reduced the likelihood of a gastrointestinal tract catastrophe

Fever returning in the very late postoperative period suggests the development of a new process rather than a complication of the operative procedure, but the persistence of the open sternotomy wound in this patient reverses the usual risks The postpericardiotomy syndrome or postpump syndrome seem most unlikely explanations for fever developing 6 months after surgery [1] Infective endarteritis has not been reported on a saphenous vein bypass but this process nonetheless seems possible There were no signs of valvular heart disease to suggest acute infective endocarditis and careful general examination revealed no evidence of infection in other organ systems such as the lungs urinary tract, or brain Pericarditis, especially purulent pericarditis could have explained pain and fever but there were no confirming features on the ECG or physical examination [3] The echocardiogram taken shortly before death (Fig 2) demonstrated an echo free space posterior but not anterior to the heart raising the possibility of a posterior loculated pericardial effusion [4]

Unfortunately the major feature suggestive of a pericardial effusion was the development of tamponade which came at the end of his brief hospital course Initially his systemic hypotension was thought to be due to septic or cardiogenic shock but the right heart pressure recordings strongly suggested cardiac tamponade i e the equally elevated pressures in diastole in all chambers of the heart (Fig 3) [6] Despite his previously opened pericardium and the unlikelihood of this developing 6 months after operation the final event clearly appeared to be pericardial tamponade

In summary the persistent chest pain high fever and circulatory shock are best explained by an infected posteriorly loculated pericardial effusion with tamponade Shortly after the pertinent data were obtained and before drainage of the pericardial effusion could be established cardiac arrest occurred from which the patient could not be resuscitated

Autopsy findings

At autopsy the kidneys were markedly enlarged by the presence of innumerable fluid filled cysts measuring up to 4 cm in diameter Each kidney weighed 1 800 grams and had no remaining normal parenchyma (Fig 4) The liver also had multiple small cysts which were of no apparent functional significance

The unclosed sternotomy wound showed granulation tissue on its margins The anterior surface of the heart was covered by fibrous adhesions The left lateral and posterior portions of the



ig 4 Coronal section of one of the markedly enlarged (1 800 rams each) kidneys with adult polycystic disease

ericardial sac contained a loculation of 300 ml of urulent exudate from which a Group A beta treptococcus was obtained on postmortem ulture The coronary arteries had severe athero clerosis with complete occlusion of the right and 0 per cent occlusion of the left anterior descend n coronary artery (Fig 5)

The saphenous vein graft to the left anterior lescending coronary artery was patent with a vell formed layer of concentric fibrous plaque on he intima of the vein graft The graft to the obtuse marginal branch of the circumflex coro ary artery showed total occlusion at the distal end of the vein to artery anastomosis but a patency of proximal end (Fig 6)

The heart had left ventricular hypertrophy and a well healed posterior left ventricular myocar dial infarct The lungs showed severe congestion and edema

Dr Grover M Hutchins It seems clear that the patient s terminal course can be ascribed to the loculated asymmetric purulent pericarditis Development of such a phenomenon following cardiac surgery requires an adherence of the margins of the opened pericardial sac to the cardiac surface The process was doubtless facili tated in this patient by mediastinitis and sternal dehiscence which complicated the postoperative course Although this infection was brought under control a bed of granulation tissue remained over the epicardial surface It is possible that infection of the posterior sac was a conse quence of mediastinitis although the interval between the two events with no symptoms of infection present was weeks We had noted a similar association of mediastinitis and prosthetic valve endocarditis in other post cardiac surgery patients

The rapid progression of the terminal course probably reflects the rate of accumulation of the exudate It is well recognized that large pericar dial effusions may accumulate if they develop slowly so that the fibrous parietal pericardium is able to stretch to accommodate the volume If the fluid accumulation is rapid as would occur with a purulent exudate the relatively rigid pericar dium leads to compression of the atria

Dr J O Neal Humphries Reviewing this man s course retrospectively it is important to recognize why his purulent pericarditis and the final tamponade were so difficult to appreciate clinically Although tamponade due to hemoperi cardium is a recognized problem in the early postoperative period it is a most unusual late complication of cardiac surgery Furthermore in part because it was a postoperative effusion and therefore not present anteriorly the usual clinical features of cardiac tamponade were not appre ciated The ECG did not show low voltage the ST T wave changes or classical electrical alterans although some variation in the ECG pattern between two sequential beats is seen (Fig 1) The heart size on chest roentgenogram did not change and the echocardiogram (Fig 2) showed no evidence of fluid anteriorly The demonstra tion of a sonolucent area posterior to the heart but not anteriorly may be seen in a patient with a small or moderate sized effusion but a large effu sion usually is evident anteriorly [4,5] An impor tant exception to this is the patient who has undergone sternotomy and pericardiotomy The pericardial sac is usually left open but postoper ative adhesions form in the anterior mediastinum and obliterate the potential anterior pericardial

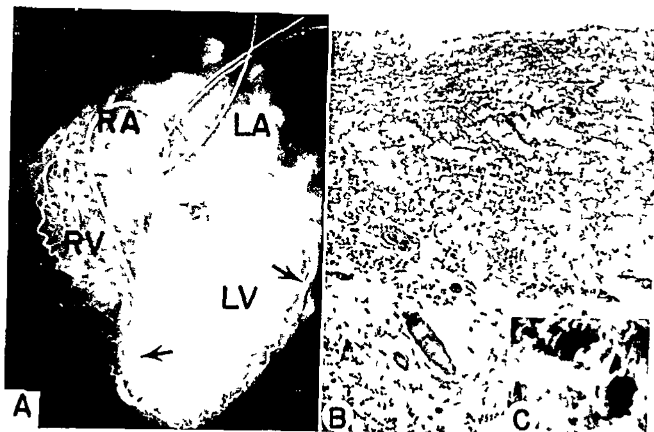


Fig 5 A Postmortem coronary arteriogram with two saphenous vein bypass grafts The vein to artery anastomosis into the left anterior descending coronary artery (lower arrow) is widely patent the distal anastomosis of vein graft to obtuse marginal branch of the left circumflex coronary artery (upper arrow) is *occluded at the downstream end* The distal portions of the obtuse marginal and right coronary artery which is occluded near its origin are filled through collateral vessels *B* Organizing fibrinopurulent epicardial exudate (Hematoxylin and eosin × 120) *C* Gram positive cocci singly and in short chains within the purulent pericarditis *(Brown & Brenn bacterial stain × 1 200)*

space Thus even the echocardiographic signs of pericardial effusion may be particularly subtle in the patient after cardiac operation

DR BERNADINE H BULKLEY In addition to the recognition of his pericardial effusion with tamponade, the second equally difficult diagnostic problem in this man s clinical course was the recognition of the infective process within the pericardial sac Purulent pericarditis is less frequent in the antibiotic era and notoriously difficult to diagnose clinically the diagnosis being made in only less than half of patients who die with this condition [11, 1] Purulent pericarditis is usually not a primary disease but is most often associated with other illnesses such as pneumonia, septicemia endocarditis and as in this patient previous trauma to the pericardial sac as with cardiac surgery Often the underlying infectious disease or systemic illness obscures the infection of the pericardium [8, 9] Definitive diagnosis is difficult to make noninvasively and pericardiocentesis generally requires a high index of suspicion In this patient in particular not only were the signs of pericardial effusion particularly subtle, but a diagnostic pericardiocentesis would have been especially difficult because of the posterior location of the fluid The history of mediastinal infection perhaps was a clue to the presence of purulent pericarditis in this man

DR J O NEAL HUMPHRIES Infective mediastinitis is one of the most serious complications of open heart surgical procedures After an uncomplicated very early postoperative period infection in the mediastinum usually presents itself from day 5 to day 10 The initial symptoms are often nonspecific and include failure to regain strength poor appetite and low grade fever Early physical findings include a fever erythema along the surgical wound and instability of the sternum as detected by palpation Purulent drainage develops several days later Once mediastinal infection is recognized the involved area must be opened and debrided Regular cleansing and packing of the wound allows healing from the deepest portion of the wound and eventual complete closure though this usually greatly delays the return to health Infection of the mediastinum develops with greater frequency in

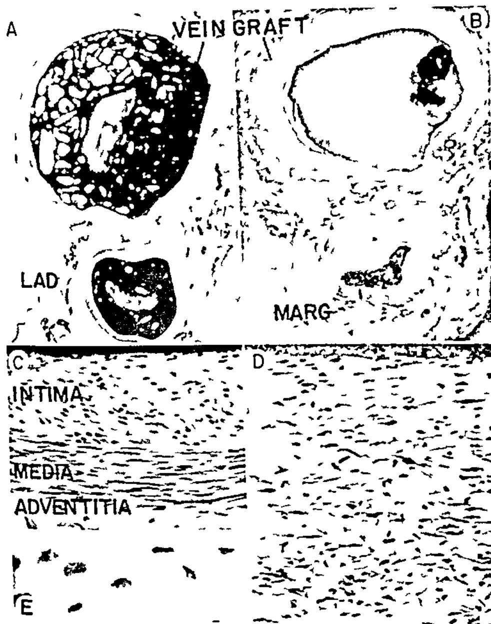


Fig 6 *A* Cross section of vein graft (above) and left anterior descending coronary artery (*LAD*) near the anastomosis (lower arrow in Fig 5 *A*) *B* Vein graft (above) and obtuse marginal coronary artery (*MARG*) near the anastomosis (upper arrow in Fig 5 *A*) Note the marked concentric intimal plaque in this vein graft with poor runoff as compared to the graft with widely patent anastomosis shown in Fig 6 *A* (*A* and *B* hematoxylin and eosin × 30) *C* Wall of the vein graft shown in Fig 6 *A* Tissue between the arrows is concentric intimal plaque formed subsequent to implantation of the graft The media and adventitia (below) show no change *D* Portion of the much thicker newly proliferated concentric fibrous plaque from the vein graft shown in Fig 6 *B* which has an obstructed downstream anastomosis (*C* and *D* hematoxylin and eosin × 300) *E* Intimal surface of vein graft showing laminar fibrin deposit with incorporated mesenchymal cells The conversion of such fibrin deposits into connective tissue appears to form the concentric fibrous plaque (Hematoxylin and eosin × 900)

patients who have been chronically ill such as this man Furthermore the presence of chronic renal failure in this patient played a significant role in the very slow healing of the mediastinal wound Postoperative mediastinitis has been recognized as predisposing to endocarditis after prosthetic valve replacement[7] and it seems likely that mediastinitis would similarly predispose to purulent pericarditis

DR BERNADINE H BULKLEY Although not directly related to the final event one of the most striking features of this man s chronic illness was

his severe premature coronary atherosclerosis He had a myocardial infarction at age 33 followed by angina pectoris By age 38, with recurrent angina intractable to medical therapy, coronary angiography demonstrated severe narrowings of each of his three major coronary arteries What are the possible explanations for his accelerated atherosclerosis? With regard to usual coronary artery disease risk factors he had a negative family history for coronary disease, he was not a smoker, and did not have diabetes mellitus He did have long standing systemic hypertension documented for at least 9 years prior to his first bout of angina pectoris Although he did not have hypercholesterolemia he did have periodic elevations of his serum triglycerides related to his chronic renal failure His underlying polycystic kidney disease, causing systemic hypertension and leading to chronic renal failure by age 25, was likely the worst of all coronary artery disease risk factors in this patient Lindner and associates[14] in a retrospective study of patients undergoing chronic hemodialysis for from 1 to 13 years, showed that cardiovascular disease in general accounted for over half of all deaths, and that deaths were in a relatively young population averaging 37 years of age

Whether what appears to be accelerated atherosclerosis in the population with chronic renal failure undergoing chronic hemodialysis is related to the treatment per se or to the underlying disease is not clear Intermittent blood pressure elevations and hyperuricemia are frequent problems in patients undergoing chronic hemodialysis Chronic hemodialysis also prolongs life in the uremic patient, thus providing prolonged exposure of his cardiovascular system to these and other recognized or possible risk factors associated with uremia such as hypertriglyceridemia, glucose intolerance and abnormalities of calcium metabolism[1,3] Despite the unusual clinical setting and variety of potential risk factors morphologically, his coronary artery lesions per se were not distinctive

Dr Grover M Hutchins At autopsy his coronary artery disease was extremely severe particularly for his age but the morphology of the coronary occlusive disease was typical for this disease An old total occlusion of his right coronary artery was present to account for his remote posterior myocardial infarct We have found that in over 95 per cent of instances a coronary occlusive lesion can be identified to account for a given anatomic infarct[1]

The saphenous vein grafts in place for only 5 months also showed a form of accelerated atherosclerosis which is commonly found in patent grafts in place for at least several weeks[1] (Fig 6) Although the intimal plaque has been suggested to be a response of the vein to systemic pressure there is evidence that the plaque may develop from thin laminar deposits of intimal thrombus[0] Of particular interest in this patient is that there was a difference in the amount of plaque developing in the two vein grafts implanted at the same time The graft into the diagonal branch had an occlusion of the distal end of the vein to artery anastomosis and the intimal change in this graft with presumably less blood flow, was thicker than the layer of fibrous plaque in the graft into the left anterior descending artery which had a widely patent anastomosis Whether these differences were related to differences in flow or pressures is uncertain Whether these fibrous plaques which are virtually indistinguishable from atherosclerosis will cause progressive vascular lumenal narrowing like natural coronary artery atherosclerosis is also awaiting the test of time

Summary

This relatively young man with a host of medical problems including polycystic kidneys chronic renal failure long standing hypertension and premature atherosclerosis died of cardiovascular disease not as might be expected from his severe coronary artery disease but rather from purulent pericarditis The latter was an unusual and unexpected consequence of the entire complex of his illnesses and because of its confinement to the posterior pericardium by postoperative adhesions produced an asymmetric cardiac tamponade

REFERENCES

1 *Ito M A and* Goldberg H P Postpericardiotomy syndrome following surgery *for nonrheumatic* heart Circulation **17** 549 1958
2 Soffer A Electrocardiographic abnormalities in acute *convalescent and recurrent* stages of idiopathic pericarditis Am Heart J **60** 729 1960
3 Surawicz B and Lasseter K C Electrocardiogram in pericarditis Am J Cardiol **26** 471 1970
4 Teichholz L F In Gramiak R and Waag R C editors Echocardiographic evaluation *of* pericardial effusion in cardiac ultrasound St *Louis* 1975 The C V Mosby Company pp 106 114

5. Spodick, D H Acute cardiac tamponade Pathologic physiology, diagnosis and management Prog Cardiovasc Dis 10 64 19
6. Shabetai, R Fowler N O and Guntheroth W G The hemodynamics of cardiac tamponade and constrictive pericarditis, Am J Cardiol 26 480 1970
7. Anderson D J Bulkley B H and Hutchins G M Prosthetic valve endocarditis in 2 patients morphologic basis for diagnosis and therapy Am Heart J (In press)
8. Rothman J Chase N F Kricheff I I Mayoral R and Berantaum E R Ultrasonic diagnoses of pericardial effusion Circulation 35 358 19
9. Feigenbaum H Echocardiographic diagnosis of pericardial effusion Am J Cardiol 26 4 5 19 0
10. Boyle J D Pearce M L and Guze L B Purulent pericarditis review of literature and report of eleven cases, Medicine 40 119 19 1
Rubin R H and Moellering R C Jr Clinical microbiologic and therapeutic aspects of purulent pericarditis Am J Med 59 68 19
12. Klacsmann P G Bulkley B H and Hutchins G M The changed spectrum of purulent pericarditis an 86 year autopsy experience with 215 patients (Abstr) Circulation (In press)
13. Roberts W C Bulkley B H and Morrow A G Pathologic anatomy of cardiac valve replacement a study of 224 necropsy patients Prog Cardiovasc Dis 15 539 19 3
14. Lindner A Charra B Sherrard D J and Scribner B H Accelerated atherosclerosis in prolonged maintenance hemodialysis N Engl J Med 290 697 1974
15. Lowrie E G Lazarus J M Hampers C L and Merrill J P Cardiovascular disease in dialysis patients N Engl J Med 290 7 1974
16. Bagdade J D Porte D Jr and Bierman E L Hypertriglyceridemia a metabolic consequence of chronic renal failure N Engl J Med 279 181 1968
17. Ridolfi R L and Hutchins G M The relationship between coronary lesions and myocardial infarcts ulceration of atherosclerotic plaques precipitating coronary thrombosis Am Heart J (in press)
18. Vlodaver Z and Edwards J E Pathologic changes in aorto-coronary arterial saphenous vein grafts Circulation 44 719 1971
19. Unni K K Kottke B A Titus J L Frye R L Wallace R B and Brown A L Pathologic changes in aortocoronary saphenous vein grafts Am J Cardiol 34 6 19 4
20. Bulkley B H and Hutchins G M Accelerated atherosclerosis A morphologic study of 91 saphenous vein coronary artery bypass grafts (abst) Am J Cardiol 37 1 19 6

Fundamentals of clinical cardiology

Sudden infant death syndrome (crib death)

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Sudden death in the adult is an event familiar to the cardiologist reflecting a cardiac origin in most cases Although it seems doubtful that the heart is primarily involved in most instances of sudden death in infancy, secondary arrhythmias may play a role In addition the ' near miss' of sudden infant death syndrome (SIDS) is sometimes referred to the cardiologist as a case of possible cyanotic congenital heart disease At the least a review of current knowledge and speculation about crib death an entity that claims 8 000 to 10 000 infants annually should be of interest to cardiologists

By definition, crib death or sudden infant death is diagnosed after autopsy by exclusion of inherently lethal pathology The death is unexpected, as well as sudden, although an upper respiratory infection may have been recognized for a day or so Death apparently occurs quietly during sleep and with very few exceptions between 1 and 6 months of age There is a significant association of SIDS with winter months lower socioeconomic class and a history of prematurity [1] Autopsy findings that are characteristic although not universal, are intrathoracic petechiae and pulmonary edema Recently Naeye has reported that these victims have thickened musculature of the small pulmonary arteries when compared with control subjects of the same age the thickness is comparable to that in infants living at high altitudes These changes and other subtle postmortem findings offer evidence of earlier hypoxia in victims of crib death

Etiology

The cause of SIDS has been guessed at for centuries The first SIDS case recorded was presumably in First Kings, where the death was attributed to the infant having been overlain by its mother (A surviving infant of the household was then claimed by the bereaved mother, Solomon s celebrated resolution of the dispute proposed to divide the remaining infant in half!) The practice of taking infants to bed with adults ultimately became unfashionable perhaps due to continued occurrences of SIDS Suffocation remained a popular explanation of the tragedy to lay coroners and was attributed to bedclothes However a normal infant placed face down on a pillow will not suffocate but will cope through head or body movements to insure an adequate airway [3] Nevertheless intrathoracic petechiae were proposed as evidence of airway obstruction by Handforth[4] in 1959 In the first animal model of crib death he produced petechiae in rats by occluding their airway and compared them to the postmortem findings in human victims of SIDS Handforth postulated laryngospasm as the lethal mechanism in infants, and this mechanism remains one of the most highly regarded by research workers in SIDS The trigger of laryngospasm has been attributed to inflammation of the larynx by viruses [5] obstruction of the nasopharynx during the period of obligatory nasal breathing [6] and a reflex laryngeal response to water One other cause of airway obstruction that deserves mention, because of the lesson inherent is status thymicolymphaticus A large thymus found in infants dying unexpectedly was thought to have partially obstructed the trachea, subsequently any large thymus found on chest x ray was actually subjected to irradiation therapy The large thymus was in fact a normal feature of a well nourished infant and the irradiation has tragically resulted in late malignancies

There is reason to doubt the inference of airway obstruction from the presence of petechiae We killed rats in various ways to determine the common factor responsible for intrathoracic petechiae and, to our surprise, abrupt and unremit

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ting airway obstruction rarely produced petechiae whereas breathing 100 per cent nitrogen caused petechiae in over 80 per cent of the animals These findings in rats were corroborated in clinical reports Petechiae are relatively infrequent in suffocation with plastic bags or foreign bodies in the airway[1] Camps[11] stated that hanging causes no petechiae, when it is abruptly effective whereas slow congestive death by hanging was usually attended by petechiae In a review of postmortem x rays of the airways of 78 victims of SIDS we found no evidence of obstruction of the nasopharynx[2] as postulated by Shaw[4] Finally none of these airway theories would account for the absence of crib death in the first month of life the predisposing conditions such as obligatory nasal breathing are most prevalent at birth and decline with increasing maturity

There have been numerous other theories of crib death most of which may be easily dismissed as a universal cause although lethal enough in rare instances Bilateral choanal atresia for example can kill in the first few hours of life since most normal infants are obliged to breathe through the nose for the first few weeks of life[11]

An immune deficiency was a popular theory prior to the first conference on SIDS in Seattle in 1963 because the immune serum globulins declined from birth to a nadir that coincided with the age of peak incidence of crib death Unfortunately for this theory the victims of SIDS actually had higher levels than normal control subjects of the same age

Congenital absence of the parathyroid glands was blamed for SIDS in an unfortunate publication devoid of embryologic or pathologic substance[5] Other pathologic studies from a variety of institutions have ruled out this anomaly as a common occurrence in SIDS and embryologically it does not make sense since the parathyroids arise from the same branchial pouch that forms the thymus An infant with the rudimentary thymus syndrome would be in difficulty with tetany in the first 1 or 2 weeks of life and this would be obvious on postmortem examination

British immunologists were (and a few still are) convinced that SIDS is a hypersensitivity reaction to cow s milk This led some to suggest that a mother is risking crib death if she does not breast feed Several centers have found no difference in titers against cow s milk in crib deaths and controls[1] [11] and at least one eighth of the victims were receiving only breast milk at the age of crib death[1]

We now come to some mechanisms that have been proposed as causing SIDS which seem of greater validity at least as contributing factors These are infection child abuse arrhythmias and apnea

Infection Overwhelming bacterial infection was the first proved cause of sudden death in infants diagnosed by postmortem culture Farber[19] proposed that unsuspected infection might prove to be the cause of most instances of what is currently diagnosed as crib death It was eventually possible to disprove sepsis as the cause in most cases of SIDS but viral infections have not been as easy to dismiss from an important role Initially Gold and colleagues[1] reported virus isolations from 25 per cent of their autopsies of SIDS The prevalence in subsequent surveys of crib death has varied literally from 0 to 100 per cent Valdes-Dapena[1] suggested that the higher rates are found during viral epidemics in which a virus may be present but not causally related to death Yet the common history of a respiratory infection and subtle postmortem findings of inflammation in the upper respiratory tract have convinced most of us that mild virus infections play some role perhaps in increasing the probability of a prolonged apneic episode

Child abuse (infanticide) Child abuse is a tragically common occurrence current estimates range from 60 000 to 400 000 cases annually in this country[20] The incidence then is from six to 50 times that of SIDS although fortunately the majority of cases are not lethal. The relevance of this problem to SIDS is that as Valdes-Dapena has carefully put it "Intentional homicidal suffocation cannot be excluded with certainty at autopsy[1] One family in Philadelphia was reported in the lay press to have lost seven infants to SIDS but the chief medical examiner in that city concluded after careful study that the deaths were *not* due to SIDS and were highly suspicious of homocide There may be clues at autopsy that point to abuse such as bruises long bone fractures abdominal hemorrhages or physical evidence of general neglect but there will be instances of uncertainty which present a terrible dilemma to the conscientious medical examiner The grief of the sudden loss of a loved infant should not be compounded by insensitive accusations but infanticide and child abuse should be

detected if for no other reason than to prevent the recurrence The horns of the dilemma are sharpened by the zeal of parent physician groups involved in crib death who have publicly attacked more than one forensic pathologist whose mistake was to infer abuse in a child who *may* have been a crib death victim [1]

Arrhythmia Sudden death in adults most often is cardiac in origin, and specifically involves ventricular fibrillation or asystole It is not unreasonable to suspect involvement of arrhythmias in SIDS In 1953 Adelson proposed that a 'reflex vagocardiac inhibition might account for the paucity of autopsy findings in SIDS A similar theory was proposed by Stowens [3] who was impressed by the frequency of pulmonary edema in crib death He proposed a 'mass reflex' of the autonomic system which involved all organs but attributed death to a lethal arrhythmia Wolf[4] was more specific in dealing with reflexes he suggested that the dive reflex might be initiated in the infant by saliva on the face and, due to an immature control system death would ensue Wolf suspected a terminal arrhythmia ventricular fibrillation and offered a situation parallel to adult noncoronary deaths due to fright

An intriguing proposal that ventricular fibrillation may cause crib death has been put forth by two groups [5, 6] They postulate a lethal expression of the long Q T syndrome (LQTS) either as an infantile form of the inherited disorder or as a developmental state with transient vulnerability Schwartz and colleagues have made a convincing case for asymmetric sympathetic innervation of the heart as the basis of the LQTS based in part on the abolition of syncopal attacks by ablation of the left stellate ganglion A congenital underdevelopment of the right stellate ganglion is suggested as the most common cause of asymmetry Schwartz proposed that there may be a similar asymmetrical condition during maturation of the normal infant and a state of increased stress such as hypoxia, might culminate in ventricular fibrillation The group at the National Heart Institute have found 26 per cent of the 42 sets of parents of SIDS victims had prolonged Q T intervals as did 40 per cent of the siblings in these same 11 families [6] They also have reported a single infant who was resuscitated successfully who was found to have a markedly long QTc As further suggestive evidence, they described 'small foci of normal sized disorganized cells in the ventricular system of 22 per cent of infants with SIDS and 12 per cent of control infants They described these abnormalities as resembling those of asymmetric septal hypertrophy (ASH) and speculated that they might serve as a nidus for ventricular arrhythmias They found three sets of parents that had both ASH and prolonged QTc

An earlier study of hearts from SIDS victims by James[7] reported focal histopathologic changes in the conduction system He proposed that these foci in the atrioventricular node and His bundle triggered lethal arrhythmias However, he found similar changes in infants of the same age who had died of known causes Valdes Dapena and her colleagues [8] concluded that the changes described by James are characteristic of supportive structures in the infant in many sites, and not evidence of rapid remodeling which should cause lethal arrhythmias

In 1967 we reported arrhythmias in 90 per cent of 30 prematures detected with the use of 6 to 12 hour tapes [11] This incidence was much greater than in term babies studied with the same technique [11] The significance of this was the additional epidemiologic data of increased prevalence of SIDS in babies prematurely born [1, 3] However the arrhythmias we found were relatively benign sinus bradycardia with and without nodal (junctional) escape compatible with an oxygen conserving (dive) reflex Also the arrhythmias decreased in severity and frequency as age and weight increased Thus the age of most frequent *arrhythmias (the first month) does not correspond* with the age of vulnerability to SIDS which spares the first month of life and peaks at 3 to 4 months

The age distribution of SIDS is also difficult to correlate with the aforementioned long QT syndrome The hereditary form would obviously not cease killing its victims at 5 or 6 months of age We have developed thorough pedigrees in three different families with LQTS and there were no deaths explained or otherwise during infancy and when syncope developed in affected members of the family it never occurred before the age of 5 years Looking at the patients that have survived a near miss of crib death we *have recorded electrocardiograms* on eight of these cases and none of them had LQTS including two that subsequently died with an autopsy diagnosis of SIDS

There are additional grounds for doubting that

ventricular arrhythmias such as occur in LQTS are a frequent cause of SIDS Premature infants often develop apnea during their time in the hospital and in most centers they are monitored continuously with ECG and pneumograph It has been extremely rare in our neonatal intensive care unit to see any arrhythmia other than bradycardia and junctional escape in these premature infants in spite of prolonged apnea and heart rates as low as 40 Two infants with frequent VPCs and episodes of sustained ventricular tachycardia were surprisingly stable in general in spite of the unstable rhythm and have survived without subsequent incident It is our conviction that a normoxic infant can survive long episodes of severe arrhythmia

In our study of the genesis of intrathoracic petechiae in rats ventricular fibrillation was induced by intraventricular injection of potassium chloride and petechiae were found in only 27 per cent of the animals in contrast to hypoxic hypoxia which produced petechiae in 87 per cent of the rats and in contrast to petechiae in 82 per cent of SIDS victims In postmortem studies of SIDS the oxygen tension in the left heart has been found to be consistently low suggesting that the heart beat continued after respirations ceased.[1] A separate autopsy study found a very high percentage of blood that was completely unclotted in SIDS which is thought to be due to continued perfusion of tissues under profoundly hypoxic conditions with attendant release of fibrinolysins These three autopsy findings—petechiae left heart oxygen and blood fluidity—are evidence that apnea occurs prior to any terminal arrhythmia

Apnea In the first conference on sudden death in infants in Seattle in 1963 most of the participants were pathologists and the emphasis was on autopsy criteria for the diagnosis of crib death I proposed that the disease spectrum should be broadened to include the living that had been resuscitated from what otherwise would resemble sudden infant death The concept of near miss was based on personal observations of in hospital infants other than premature infants that were discovered to be apneic and cyanotic but with marked bradycardia who recovered after mouth to mouth resuscitation and who subsequently survived in a completely normal state There has been a gradual acceptance of this broader view of crib death which led to the adoption of the current term sudden infant death syndrome with the second conference in Seattle in 1969 There are still skeptics who question whether there is any relationship between the near miss and crib death and in a given infant it is impossible to prove whether an infant might have recovered even without intervention or that a dead infant *could* have been resuscitated at an opportune instant Still the autopsy findings of SIDS are by definition less than lethal and therefore compatible with resuscitation Conversely a limp cyanotic baby with apnea and profound bradycardia could certainly be expected to die by standards of ordinary common sense and the postmortem findings would be compatible with SIDS Additional evidence may be found in the follow up of near misses at least two of them (out of an estimated 20) have returned dead on arrival to Children s Orthopedic Hospital in Seattle and an autopsy diagnosis of SIDS was made[3] Other centers have reported similar experience recurrences are not common but the frequency is much greater than in the normal population of the same age (approximately 2 per 1000)

With the acceptance of the near miss as an intergral part of the sudden infant death syndrome apnea has become the focus for an increasing number of workers in this field Although Wolf's central concern with the dive reflex was lethal arrhythmias that reflex begins with apnea mediated through a cold or wet stimulus to the trigeminal nerve We tested for this reflex in infant monkeys as an animal model for SIDS The infant monkeys with cold or wet stimuli to the cheek became apneic and developed bradycardia within 1 or 2 seconds The blood pressure remained unchanged unless atropine was given to block the bradycardia with atropine hypertension developed demonstrating vasoconstriction No arrhythmias other than those of a sinus mechanism were noted The only malfunction of the reflex was seen in two instances of failure to resume respiration when the stimulus was removed requiring external ventilation to restore spontaneous activity When the monkeys were tested again at 2 to 3 months of age comparable to over 6 months of age for the human being they resumed respiration promptly when the dive stimulus was removed Thus the oxygen conserving dive reflex in infants seems to function in a protective and effective way with

persistence of the apnea as the potentially lethal error of the system [36] This suggested to us that the vulnerability of the infant was the apparent readiness to return to a fetal like state of apnea, a frequent event during sleep in the normal premature infant [37] A study by McGraw [38] in 1939 suggested that the normal infant in the first 4 or 5 months is quite at home submerged in water She observed rhythmical, coordinated, and propulsive swimming movements in the prone submerged young infant, whereas after 5 or 6 months of age, the same infants would cough struggle and had ineffective, poorly coordinated limb movements The younger infants she described as having excellent breath control' This lack of alarm (or arousal in the sleeping infant) during apnea may be a lethal error if primary apnea occurs from some nonspecific stimulus

Sleep is an almost universal part of the story of SIDS epidemiologically although the evidence is circumstantial In the 1963 conference the inference of sleep was drawn from the time of discovery of the dead infant In the 1969 conference Bergman argued that the data collected in King County indicated that 100 per cent of the SIDS victims died in their sleep [illegible] although others have reported autopsied instances of SIDS in which the infant was being fed or in a stroller and was seen to stiffen out stop breathing and become cyanotic In our experience we have observed two near misses' with observed seizure disorders one tonic and one clonic and who had postictal apnea which required ventilatory resuscitation Again we believe there are a number of causes of primary apnea at this age, the crucial aspect appears to be the resumption of spontaneous respiration Nevertheless sleep probably plays an important role in most instances of SIDS In the 1969 conference I [1] pointed out (1) the depression of ventilation in relation to arterial CO_2, with sleep in the normal adult, (2) the sleep apnea that occurs in 'normal prematures, and (3) the sleep apnea in certain abnormal states which could be fatal, known as 'Ondine s curse, and proposed apnea monitoring for the 'near miss' Steinschneider [40] however was the first investigator to provide substantial clinical observations of infants during prolonged apnea in 1972 He monitored respiratory activity during sleep in five infants who were referred because of cyanotic episodes They were all observed to have a number of prolonged apneic spells with cyanosis during sleep, some of which required vigorous resuscitative efforts Of particular interest, upper respiratory infections were associated with an increase in frequency of these episodes of prolonged apnea, and two of the infants died subsequently of SIDS Although Steinschneider reported that apnea was associated with rapid eye movement (REM) sleep he included episodes of apnea as short as 2 seconds, which probably caused inclusion of periodic respirations in his apneic" episodes His patients and others previously reported [39] demonstrate that at least some of the victims of crib death have had previous episodes, this is consistent with the subtle postmortem evidence of prior hypoxia reported by Naeye This year the Stanford group have confirmed Steinschneider s data on sleep apnea in prematures and 'near misses' [41] except for the association of prolonged apnea with quiet (NREM) sleep in the newer study, brief episodes of apnea labeled respiratory pauses were associated with REM sleep Guilleminault s group recorded both airflow and chest movement They found, in addition to the usual central apnea with no muscular activity upper airway apnea" in which chest movement continues but with no air exchange Upper airway apnea not only caused a more rapid fall in oxygen saturation but it would escape detection if the infant s respiration were monitored only with a pneumograph

The Stanford group hypothesized arrhythmias as the final lethal disorder terminating sleep apnea in crib death [41] However the only details of cardiac arrhythmias which have been published do not support this contention Marked bradycardia was present in 11 of 12 patients with sleep apnea [4] but as had been proved, bradycardia is an essential component of the oxygen conserving response [42] They reported only one patient with ventricular tachycardia [4] and apparently no other sustained ectopic arrhythmias Although death obviously includes cardiac arrest which must be classed as the ultimate arrhythmia agonal events should not be confused with earlier reversible stages of the sequence

The adult patients with sleep apnea had earlier been reported by Guilleminault Eldridge and Dement [43] as one aspect of primary sleep disorders They discovered, in 10 per cent of a large group of patients complaining of insomnia that the primary problem was sleep apnea In sleep they developed surprisingly long periods of apnea



Fig 1 Record of respiration with a pneumograph airway flow with a pneumotachometer arterial pressure (torr) Pa_{CO_2} (torr) and arterial oxygen saturation (per cent) in a dog subjected to airway occlusion After apnea occurred the airway was opened to room air Apnea was interrupted after 80 s by spontaneous gasping which produced an increase in saturation and after two further apenic episodes, regular respirations resumed when the oxygen saturation had reached a level of 40 to 50 per cent. High amplitude gasps gradually decrease in frequency but are still occurring when the arterial saturation has returned to normal (Reproduced from the J Clin Invest. 56 1371 1975 with permission)

terminated by arousal These episodes of apnea occurred often enough to produce pulmonary hypertension apparently through hypoxia It seems unlikely that middle aged adults such as these subjects who have survived years of apneic episodes would be less vulnerable to arrhythmias than infants who are free of degenerative disease Rather the crucial difference between life and death is more likely the ability of the adult to arouse and terminate the apnea based on internal alarms We proposed after our study of the immature monkey that the immature human infant after 9 months of fetal apnea had not *learned* to be alarmed by apnea and its consequences In the adult it appears that hypercarbia is alarming but hypoxia is not If an underwater swimmer hyperventilates sufficiently prior to a prolonged apneic swim he is in danger of losing consciousness and drowning due to insidious hypoxia (Certain forms of hypoxia are alarming such as breathing gas mixtures with low oxygen content but the unpleasantness is perceived through the proprioception of increased respiratory effort

The role of deep sleep in apnea was also confirmed from studies in kittens McGinty and Harper reported that sleep deprivation caused a significant increase in the frequency of apnea when the kitten was permitted to sleep This difference was most pronounced in the youngest group They speculated that human upper respiratory infections might operate through sleep deprivation in producing the increased frequency of apnea that Steinschneider had previously reported Sleep when it does occur may be more difficult to arouse from arousal disorders are thought to be basic to other sleep disorders of childhood—eneuresis and night terrors

To relate sleep apnea and a range of reflexes that initiate apnea to SIDS it is helpful to consider these as various forms of primary apnea We proposed that there are probably multiple pathways that *initiate* apnea which would be relatively brief in the older infant or adult but in the immature infant failure to resume respiration may occur and sufficient hypoxia might develop to *maintain* apnea We referred to this as hypoxic apnea because we could produce apnea in the experimental animal including rats dogs and infant and adult monkeys when the arterial Po_2 dropped below 10 torr regardless of the Pco_2 or pH[30] This was not respiratory failure or an agonal state the animal required only one or two inflations of the lung to restore normal respira

tions This hypoxic apnea persists, with a stable cardiovascular state, for 1 to 2 minutes After that time if there is no intevention either gasping occurs or the blood pressure falls and death ensues The gasp is extraordinarily effective in restoring the arterial oxygen (Fig 1), if the cardio vascular system is still intact, however, that will not be the case in the human being except for the neonatal infant who has sufficient residual anerobic capacity We propose that this capacity is what accounts for the hiatus of crib death that spares the first 3 or 4 weeks of life, during that period the apneic infant s gasp can successfully autoresuscitate The sequence of primary apnea, hypoxia apnea and successful gasp may also account for Naeye s pathologic evidence of survival of previous experience with hypoxia The lack of anerobic capacity in the adult relates to the phenomenon seen in an adult drowning victim Hypoxic apnea accounts for the absence of respiration when the victim is removed from the water promptly, artificial respiration is necessary to restore Pa_O to a level above 20 torr, at which time the victim will spontaneously breathe again If none is provided gasping in the adult will occur too late after cardiovascular collapse and death will result

The role of hypoxia in respiratory control has been neglected in most models of respiratory control and when included hypoxia was treated as only modifying the slope of the ventilation/ Pco curve It was stated that even during intense hypoxia respiratory drive continues to be controlled by pH and Pco When Pa_O was included as a controller of ventilation it was assigned a conventional negative feedback i e the lower the Pa_O the greater the respiratory stimulus mediated through the carotid body Until 1975 only nonquantitative references could be found dealing with the depressing effects of hypoxia on the medullary respiratory center Milhorn described apnea with asphyxiation simply as failure of the control system In 1975 Morrill and associates reported 19 torr as the alveolar Po at which depression occurs but they did not continue the hypoxia to the point of apnea Our finding of apnea below a Pa_O of 10 indicates that there is a narrow range of positive feedback between depression and apnea Apnea will persist below 10 torr and at Pa_{O_2} of less than 5 gasping will originate from an extraordinarily hypoxia resistant medullary center which is separate functionally from the main respiration center Gasping will continue until the arterial oxygen is sufficient to restore the activity of the normal medullary respiratory center or until circulatory failure ends life

Prevention and treatment

Treatment of the apneic cyanotic infant is obviously ventilation preferably with increased oxygen content If there is no heart beat resuscitation would be possible only with circulatory assistance through closed chest massage, although there is obviously great risk in reviving an infant badly damaged by hypoxia There should be no question however that ventilation has unchallenged priority In our opinion catechol amines have limited usefulness in resuscitation of infants if they are used they should be used in much smaller dosage than has generally been advocated We suggest that epinephrine or isoproterenol dosage should not exceed 5 μg per kilogram per minute (The usual vial contains 1 000 μg per milliliter!) Similarly bicarbonate should *not* be repeated unless a pH has been determined (The best treatment for respiratory acidosis is respiration)

If the patient cannot be resuscitated or is found dead in the crib the physicians and nurses involved should give their full support to the parents The impact of a totally unexpected death of a loved infant seems far greater with more potential for abnormally expressed grief than is usually seen with, for example an infant dying after heart surgery The first step is to obtain a thorough autopsy to establish a diagnosis If there are no lethal diseases or injuries and the age group and minimal changes are consistent a positive diagnosis of SIDS should be concluded, and most importantly the family should be promptly told and reassured that this is an entity and is not mysterious or due to neglect The opportunity for guilt is enormous and in many instances follow up visits and even counseling may be wise There are parent organizations that are ready to help with a kind of group therapy in many communities *

If the infant is resuscitated subsequent management may prove taxing There is no disagreement that the surviving near miss should

The National Foundation for Sudden Infant Death 1501 Broadway New York N Y 10036 (71)563 4630 The International Guild for Infant Survival 6822 Brompton Road Baltimore Md 21207 (301)944 2507 and the Canadian Foundation for the Study of Infant Deaths 4 Lawton Blvd Toronto Ontario M4B 1Z4 Canada (416)967 1314

be admitted to the hospital preferably in the neonatal intensive care unit and placed on a monitor In most institutions both respiration and heart rate will be monitored but from the data on upper airway apnea it follows that an apnea monitor alone may not activate an alarm until hypoxic apnea has occurred We therefore would prefer a cardiac monitor with an alarm for bradycardia under 80 which lasts for 10 seconds or greater After 2 or 3 days the question of discharge of the infant arises The concerned parent will inquire as to possible recurrences and the facts indicate there is a much greater chance than in an infant without a prior apneic episode One can argue that the chance of recurrence is still not great enough to mandate unusual management but the uncertainty will be enough to create an unbearable anxiety in many parents It is unreasonable and likely to create a schizoid survivor to keep the infant in the hospital until 6 months of age The alternative to hospitalization on one extreme and to a *laissez faire* on the other is the use of a home monitor We have monitored a half dozen near misses and prefer a simple cardiac monitor They are available in an inexpensive form that is completely portable and battery operated and one can use disposable electrodes or cheaper conventional ones The gentle click with each heart beat is reassuring to parents at night that the unit is functioning as opposed to the ambiguity of a unit that has only an alarm silence could mean either machine failure (and possible death) or that the infant is well The parents should be given explicit training in cardiopulmonary resuscitation although simple cutaneous stimulation is adequate to restore ventilation in most instances Although the situation is undoubtedly anxiety producing it seems totally unjustified to blame the anxiety on the monitor our parents have felt that their anxiety would have been far worse even intolerable without the monitor It should be emphasized to parents that the period of risk is limited to the first 5 or 6 months of life and that the child can be expected to be perfectly normal thereafter and hopefully the infant will not become a vulnerable child with long lasting emotional disorders

The widespread objection to the use of home monitors is based partly on the concern of creating anxiety which to us seems badly misdirected when a near miss has occurred the anxiety exists whether or not a monitor is used The other objection has a rather complicated well intentioned basis which is al o mi guided in our opinion The National Foundation for SID understandably wishes to minimize or eliminate any sense of guilt in the parents of crib death victims They assert repeatedly that SIDS can be neither predicted nor prevented Any public advocacy of infant monitoring is vigorously resisted by this group and has led even the American Academy of Pediatrics to take an official stand against home monitoring as being without substantial basis Assuredly no one would like to see a thousand normal infants attached to monitors continuously for 6 months to prevent two instances of SIDS but there is a middle ground that should countenance home monitoring for certain high risk infants It further should be our goal to better define the group at risk prior to death or a harrowing near miss Steinschneider has proposed a rather complicated multiple regression score and has had reasonable success although the system would be very difficult to implement on a broad scale At present an infant between 1 and 5 months of age who was prematurely born who developed an upper respiratory infection is a reasonable candidate for a cardiac monitor for a couple of weeks

In pharmacologic terms there is much less sentiment for intervention than for monitoring Yet there is substantial ground for hope First if SIDS does represent an arousal disorder then the xanthines might prove useful Xanthines have proven useful in the treatment of apnea of prematurity which is no surprise to internists who have successfully treated Cheyne Stokes respiration with caffeine Other forms of arousal disorders such as eneursis in the older child have responded to imipramine However caution in the use of any stimulant must follow the experimental results of increased frequency and severity of apnea after sleep deprivation

To sum up there is a growing consensus that apnea is the primary disorder in SIDS It is now possible to prevent at least a few of these tragedies and by cautious testing perhaps extend our abilities to better define the infant at risk For now we can confidently recommend some advice our mothers knew to be sound for infants avoid contact with too many people particularly during the cold season and do not lose sleep!

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Summary

Sudden infant death syndrome (SIDS) is diagnosed by the absence of lethal autopsy findings or in a resuscitatable, 'near miss' form with cyanosis apnea, and bradycardia The event is unexpected although a minor respiratory infection is common and occurs during sleep, between 1 and 6 months of age There is growing evidence that the victims have had previous hypoxic episodes Although suffocation is no longer considered a tenable explanation, other forms of airway obstruction are still postulated by many, the evidence however favors hypoxia as the common feature

A lethal arrhythmia has been proposed by several groups based on inappropriate reflex activity pathology ' of the conduction system and the long QT syndrome but the evidence is against arrhythmia as the primary event in most cases of SIDS

Based on the reversible near miss apnea is likely as the primary event in SIDS Several reflexes have the ability to produce apnea in addition to the relatively common sleep apnea the crucial aspect rather appears to be the failure of the immature infant to *resume* respiration The possibility exists that the infant who did not have to breathe for 9 months of fetal life, literally is not alarmed and aroused by the persistance of apnea In human and animal studies respiratory infections and sleep deprivation have been proved to increase the likelihood and duration of sleep apnea If primary apnea continues for long (45 seconds or more) a dangerous positive feedback develops into hypoxic apnea This will persist until circulatory failure occurs or until gasping occurs The gasp is a highly effective mechanism at birth but will occur too late for autoresuscitation after the anerobic capacity of fetal life diminishes we believe this capacity lasts for approximately 1 month accounting for the hiatus of crib death sparing the first month

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REFERENCES

1 Valdes Dapena M A Sudden and unexpected death in infancy A review of the world literature 1954 66 Pediatrics **39** 123 1967

2 Naeye R L Pulmonary arterial abnormalities in the sudden infant death syndrome N Engl J Med **289** 1167 1973

3 Woolley P V Mechanical suffocation during infancy Relation to total problem of sudden death J Pediatr **26** 572 1945

4 Handforth C P Sudden unexpected death in infants Can Med Assoc J **80** 872 1959

5 Beckwith J B Observations on the pathological anatomy of the sudden infant death syndrome *in* Bergman A B Beckwith J B and Ray C G editors Sudden infant death syndrome Seattle 1970 University of Washington Press pp 83 132

6 Shaw E B Sudden unexpected death in infancy syndrome Am J Dis Child **116** 115 1968

7 Dawes G S Developmental physiology *in* Robinson R R editor SIDS 1974 Toronto Ontario 1974 Canadian Foundation for the Study of Infant Deaths p 273

8 Downing S E and Lee J C Laryngeal chemosensitivity A possible mechanism for sudden infant death Pediatrics **55** 640 1975

9 Guntheroth W G The significance of pulmonary petechiae in crib death Pediatrics **52** 601 1973

10 Marshall T K Significance of petechiae *in* Bergman A B Beckwith J B and Ray C J editors Sudden infant death syndrome Seattle 1970 University of Washington Press pp 122 125

11 Camps F F Discussion in Session 3 *in* Camps F E and Carpenter R G editors Sudden and unexpected deaths in infancy (cot deaths) Bristol 1972 John Wright & Sons p 71

12 French J W Beckwith J B Graham C B and Guntheroth W G Lack of postmortem radiographic evidence of nasopharyngeal obstruction in the sudden infant death syndrome J Pediatr **81** 1145 1972

13 Beinfield H H A forgotten cause of infant suffocation J Int Coll Surg **22** 447 1954

14 Valdes Dapena M Eichman M F and Ziskin L Sudden and unexpected death in infants I Gamma globulin levels in the serum J Pediatr **63** 290 1963

15 Geertinger P The parathyroids in sudden unexpected death in infancy Acta Pathol Microbiol Scand **66** 268 1966

16 Parish W W Barrett A M Coombs R R A Gunther M and Camps F E Hypersensitivity to milk and sudden death in infancy Lancet **2** 1106 1960

17 Gold E and Godek G Antibody to milk in serum of normal infants and infants who died suddenly and unexpectedly Am J Dis Child **102** 542 1961

18 Farber S Fulminating streptococcus infections in infancy as a cause of sudden death N Engl J Med **211** 154 1934

19 Gold E Carver D H Heineberg H Adelson L and Robbins F C Viral infection A possible cause of sudden unexpected death in infants N Engl J Med **264** 53 1961

20 Green F C Child abuse and neglect Pediatr Clin North Am **22** 329 1975

21 Helpern M Medical examiners and infant deaths N Engl J Med **287** 1050 1972

22 Adelson L Possible neurological mechanisms responsible for sudden death with minimal anatomical findings J Forensic Med **1** 39 1953

23 Stowens D Sudden unexpected death in infancy Am J Dis Child **94** 674 1957

24 Wolf S Sudden death and the oxygen conserving reflex AM HEART J **71** 840 1966

25 Schwartz P J Experimental production of long QT

syndrome and SIDS Presented at Workshop of SIDS Grantees, Washington D C 1975
26. Maron B J Clark, C E Goldstein R E Fisher R S and Epstein S E Sudden infant death syndrome Potential cardiac mechanisms, Circulation 52 II-44 1975
27. Schwartz P J Periti, M and Malliani, A The long QT syndrome AM. HEART J 89 378 1975
28. James, T N Sudden death in babies New observations in the heart Am J Cardiol. 11 479 1968
29. Valdes-Dapena M A Greene M Basavanand N., Catherman R and Truex R C The myocardial conduction system in sudden death in infancy N Engl. J Med 289 1179 1973
30. Church, S C Morgan B C Oliver T K., and Guntheroth W G Cardiac arrhythmias in premature infants An indication of autonomic immaturity? J Pediatr 71 542 1967
31. Morgan B C and Guntheroth, W G Cardiac arrhythmias in normal newborn infants J Pediatr 67 1199 1965
32. Peterson D R Sudden unexpected death in infants, Am J Epidemiol 84 478 1966
33. Patrick J R Cardiac or respiratory death *in* Bergman A. B Beckwith J B and Ray C J editors Sudden infant death syndrome Seattle 1970 University of Washington Press p 130
34. Guntheroth W G Wedgwood R J and Benditt E P editors Discussion in Sudden death in infants (first conference) Public Health Service Publication No 1412 Government Printing Office 1963 p 6
35. Bergman A B in Bergman A B Beckwith J B Ray C J editors Sudden infant death syndrome Seattle 1970 University of Washington Press pp 48-49
36. French, J W Morgan B C and Guntheroth W G Infant monkeys—A model for crib death, Am J Dis. Child 123 480 1972.
37. Sinclair J C The premature baby who "forgets to breathe" N Engl J Med 282 508 1970
38. McGraw M B Swimming behavior of the human infant J Pediatr 15 485 1939
39. Guntheroth W G Some physiologic considerations, *in* Bergman A B Beckwith J B and Ray C J editors Sudden infant death syndrome Seattle 1970 University of Washington Press p 199
40. Steinschneider A Prolonged apnea and the sudden infant death syndrome Clinical and laboratory observations Pediatrics 50 646 1972
41. Guilleminault C Peraita R Souquet M and Dement W C Apneas during sleep in infants Possible relationship with sudden infant death syndrome Science 190 677 1975
42. Tilkian A G Guilleminault C Schroeder J S Lehrman K Simmons F B and Dement W C Sleep-induced apnea syndrome Reversal of serious arrhythmias after tracheostomy Circulation 51 52 II 131 1975
43. Ferrante F L Oxygen conservation during submergence apnea in a diving mammal the nutria Am J Physiol 218 363 1970
44. Guilleminault C Eldridge F L., and Dement, W C Insomnia with sleep apnea A new syndrome Science 181 856 1973
45. Craig A B Jr Underwater swimming and loss of consciousness, J A M A 176 255 1961
46. West D W M Christopher G F., and Campbell F J M Ability of man to detect increases in his breathing, J Appl. Physiol 39 372 1975
47. McGinty D J and Harper R. M Sleep physiology and SIDS Animal and human studies, *in* Robinson R R editor SIDS 1974 Toronto Ontario 1974 Canadian Foundation for the Study of Infant Deaths, p 201
48. Broughton R J Sleep disorders Disorders of arousal? Science 159 1070 1968
49. Guntheroth, W G Primary apnea hypoxic apnea and gasping *in* Robinson R R., editor SIDS 1974 Toronto Ontario 1974 Canadian Foundation for the Study of Infant Deaths p 243
50. Guntheroth W G and Kawabori I Hypoxic apnea and gasping J Clin Invest 56 1371 1975
51. Grodins, F S., Gray J S., Schroeder K R Norris, A L., and Jones, R W Respiratory responses to CO inhalation. A theoretical study of nonlinear biological regulator J Appl. Physiol 7 283 1954
52. Honda, Y., Natsui, T Hasamora N and Kakamura K Threshold Pco for respiratory system in acute hypoxia of dogs, J Appl. Physiol. 18 1053 1963
53. Gray J S The multiple factor theory of respiratory regulation Army Air Force School of Aviation Medicine Project No 386 Reports 1 2, 3 1945
54. Sorensen S C The chemical control of ventilation Acta Physiol Scand Suppl. 316 1 1971
55. Milhorn H T Jr The application of control theory to a "disease" state (Cheyne-Stokes breathing) *in* The application of control theory to physiological systems Philadelphia 1966 W B Saunders Company
56. Morrill C G., Meyer J R., and Weil J V Hypoxic ventilatory depression in dogs J Appl. Physiol 38 143 1975
57. Jansen A H and Chernick V Cardiorespiratory response to central cyanide in fetal sheep J Appl. Physiol 37 18 1974
58. Guntheroth W G Neonatal and pediatric cardiovascular crises J.A.M.A 232 168 1975
59. Committee on Infant and Preschool Child Home monitoring for sudden infant death Pediatrics 55 144 1975
60. Bergman A. B Beckwith J B., and Ray C G The apnea monitor business Pediatrics 56 1 1975
61. Shannon, D C Gotay F Stein I M Rogers, M C Todres I D and Moylan F M B Prevention of apnea and bradycardia in low birthweight infants Pediatrics 55 589 1975

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REFERENCES

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2 Naeye R L Pulmonary arterial abnormalities in the sudden infant death syndrome N Engl J Med 289 1167 1973

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6 Shaw E B Sudden unexpected death in infancy syndrome Am J Dis Child 116 115 1968

7 Dawes G S Developmental physiology in Robinson R R editor SIDS 1974 Toronto Ontario 1974 Canadian Foundation for the Study of Infant Deaths p 273

8 Downing S E and Lee J C Laryngeal chemosensitivity A possible mechanism for sudden infant death Pediatrics 55 640 1975

9 Guntheroth W G The significance of pulmonary petechiae in crib death Pediatrics 52 601 1973

10 Marshall T K Significance of petechiae in Bergman A B Beckwith J B and Ray C J editors Sudden infant death syndrome Seattle 1970 University of Washington Press pp 122 125

11 Camps F E Discussion in Session 3 in Camps F E and Carpenter R G editors Sudden and unexpected deaths in infancy (cot deaths) Bristol 1972 John Wright & Sons p 71

12 French J W Beckwith J B Graham C B and Guntheroth W G Lack of postmortem radiographic evidence of nasopharyngeal obstruction in the sudden infant death syndrome J Pediatr 81 1145 1972

13 Bonfield H H A forgotten cause of infant suffocation J Int Coll Surg 22 447 1954

14 Valdes Dapena M Eichman M F and Ziskin L Sudden and unexpected death in infants I Gamma globulin levels in the serum J Pediatr 63 290 1963

15 Geertinger P The parathyroids in sudden unexpected death in infancy Acta Pathol Microbiol Scand 66 268 1966

16 Parish W W Barrett A M Coombs R R A Gunther M and Camps F E Hypersensitivity to milk and sudden death in infancy Lancet 2 1106 1960

17 Gold E and Godek G Antibody to milk in serum of normal infants and infants who died suddenly and unexpectedly Am J Dis Child 102 542 1961

18 Farber S Fulminating streptococcus infections in infancy as a cause of sudden death N Engl J Med 211 154 1934

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20 Green F C Child abuse and neglect Pediatr Clin North Am 22 329 1975

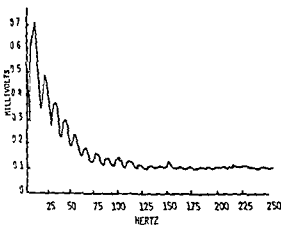
21 Helpern M Medical examiners and infant deaths N Engl J Med 287 1050 1972

22 Adelson L Possible neurological mechanisms responsible for sudden death with minimal anatomical findings, J Forensic Med 1 39 1953

23 Stowens, D Sudden unexpected death in infancy Am J Dis Child 94 674 1957

24 Wolf S Sudden death and the oxygen conserving reflex Am Heart J 71 840 1966

25 Schwartz P J Experimental production of long QT



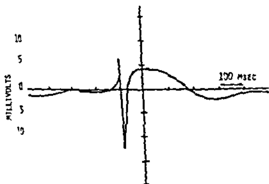


Fig 1 *Upper* Fourier transform of a typical acute ventricular unipolar electrogram *Lower* Original electrogram The portion between crossings of the isoelectric line was analyzed (Authors data analysis courtesy of Medtronic Corp Redrawn)

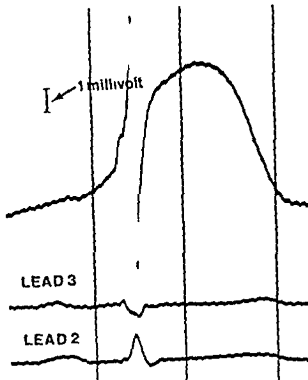


Fig 2 Typical acute unipolar electrogram of the biphasic variety Note that the intrinsic deflection (ID) appears late when compared to the peripheral ECG and that "late sensing" will occur

nology of waveform analysis Such signals by means of the Fourier Transform can be recast into the mathematically equivalent frequency domain and be visualized as a spectrum or plot of amplitude versus sinusoidal frequency [5] Both representations are equally accurate and precise and each offers specific conveniences The frequency domain form is useful to designers of electronic circuitry but as the time domain form preserves the morphologic features of the wave form it permits correlation of physiologic events with sensing circuit response As the frequency domain offers no further insights into the electro physiologic process it will not be used in this presentation (Fig 1)

Findings

The ventricular endocardial unipolar signal A majority (58 per cent) of unipolar electrograms have an ID which is biphasic with roughly equal R and S waves (Fig 2) while 30 per cent are predominately *monophasic negative* and 12 per cent are *monophasic positive* The current of injury appears as an elevated S T segment at the time of acute implant and later disappears leaving an isoelectric chronic S T segment In 68 per cent of chronic patients the ID is biphasic and in the remainder it is monophasic negative (Fig 3) (Table I) A statistically significant decrease of slew rate occurs as the electrode becomes chronic the decrease in voltage is not significant The maturing electrode may therefore have a sub threshold signal i e lacking adequate amplitude or rate of development or both to trigger a pulse generator properly (Fig 4)

The atrial endocardial unipolar signal The atrial ID is morphologically similar to the ventricular ID Its timing relative to the peripheral P wave depends on the electrode s proximity to the SA node Biphasic ID s occurred in 89 per cent of coronary sinus recordings 11 per cent were monophasic positive and none were mono phasic negative Far field ventricular potentials were comparable in amplitude but *not in slew*

A easonable analogy is of a television signal, transmitted as a band of frequencies transformed at the receiver to its visual equivalent

Cardiac pacing and pacemakers III Sensing the cardiac electrogram

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In order to understand properly those characteristics of the ventricular and atrial electrograms which trigger the implanted cardiac pacemaker, their recording and analysis was undertaken Recordings were made with high impedance physiologic preamplifiers* during initial pacemaker implantation (acute) and at pulse generator replacement at least six months and as long as 83 months after initial electrode implant (chronic) All electrodes were commercially available for routine clinical use and of 8 to 87 mm surface area No modification of procedure other than recording of the electrogram (now routinely performed) was undertaken One thousand five hundred electrograms were available and a random subset was analyzed

The electrograms were recorded in the configuration of final pulse generator connection Unipolar electrograms were referenced to a subcutaneous steel plate at the pacer site Ventricular and atrial transvenous and epicardial leads were included in the evaluation with consistent findings in all varieties Each electrogram was recorded at 200 mm /sec paper speed simultaneously with a peripheral ECG lead, usually Lead II to correlate intracardiac events with those recorded peripherally

The electrograms were analyzed for

1 Configuration (morphology) of the depolarization wave (QRS or P)

2 Amplitude dv/dt (rate of development or slew rate), duration and timing relative to the peripheral QRS of that component of the electrogram called the Intrinsic Deflection ' (ID)

3 Presence of injury and repolarization (S T segments and T) waves

In both the atrial and ventricular signals, three bioelectric phenomena were identified as contributors to the electrogram

1 The ' Intrinsic Deflection (ID) described by Lewis' and Wilson is the rapid biphasic portion which occurs as the muscle adjacent to the electrode becomes electronegative with the passing depolarization wave It exhibits the highest slew rate of the electrogram and is the only component with a sufficiently rapid voltage change (or high frequency content) to trigger a modern pacemaker It bears no relationship to the peripheral ECG since it indicates the electrical activity of only a very small area of the heart

2 ' Far field potentials which arise from electrical activity distant from the electrode' and include contralateral ventricular activation skeletal muscle potentials, and external electromagnetic interference (EMI) In the atrial electrogram the ID indicates atrial activation and the ventricular potentials are far field and conversely

3 The Current of Injury appears as an elevation immediately following the ID in acute electrograms only Believed due to a small area c damaged endocardium caused by irritation fron the electrode,' it lessens as time passes and i rarely seen in the chronic electrogram

Signals which vary with time (e g ECG s electrograms sine waves) are displayed as plots o amplitude as a function of time and are said to be in the time domain in the mathematic termi

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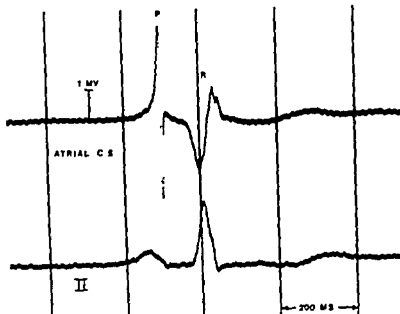


Fig 5 An atrial electrogram from the coronary sinus. The intrinsic deflection occurs well into the Lead II P wave. The ventricular complex is a far field signal with neither the amplitude nor the slew rate to trigger a pacemaker

Table IV Respiratory variations

	Unipolar		Bipolar	
	Maximum voltage (%)	Slew rate (%)	Maximum voltage (%)	Slew rate (%)
Right atrium	± 9.[illegible]	± 19	± 11.5	± 16.4
Right ventricle	± 5.3	± 6.6	± 9.4	± 10.3

Table V Epicardial unipolar chronic right and left ventricle electrograms

	Amplitude (mv)			Slew rate (volts/sec)			No of cases
	Mean		Standard deviation	Mean		Standard deviation	
Left ventricle	18.00	±	8.69	[illegible]	±	0.9[illegible]	9
Right ventricle	11.21	±	8.4[illegible]	1.09	±	0.[illegible]	14

a difference between the mean unipolar and bipolar values

2 mean ID durations shortened by 28 per cent

3 mean injury currents attenuated by 37 per cent

4 mean T waves attenuated by 34 per cent

The only disadvantage of the bipolar configuration is the possibility of ID attenuation or cancellation if the two electrodes become oriented at right angles to the direction of the propagating depolarization waves. In the clinical series the bipolar ID was smaller than the simultaneous tip unipolar signal in 51 per cent with 2 per cent of bipolar signals too small to be sensed while the simultaneous unipolar was of adequate amplitude. In 43 per cent the bipolar ID was larger and in 6 per cent the two unipolar and bipolar were equal. Bipolar injury currents (S T elevation) and far field potentials were smaller than unipolar in 96 per cent.

In canine studies atrial endocardial bipolar electrodes had attenuated adjacent ventricular potentials by 80 per cent relative to the simultaneous corresponding unipolar signals. From both atrial and ventricular leads the bipolar ID was morphologically dissimilar to the simultaneous unipolar ID yet the mean amplitudes and slew rates were equal. The bipolar ID had two sections of high slew rate resembling a monophasic triangular "spike" in 69 per cent of ventricular signals and in 50 per cent of atrial signals.

Respiration effects Respiration has a modest cyclic effect on the ventricular endocardial elec

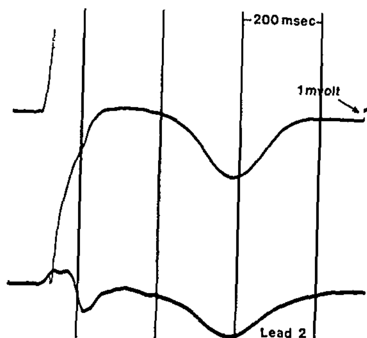


Fig 3 Typical chronic ventricular unipolar electrogram of the biphasic variety Note the isoelectric S T segment and the appearance of the intrinsic deflection (ID) at the beginning of the peripheral ECG so that normal sensing will occur

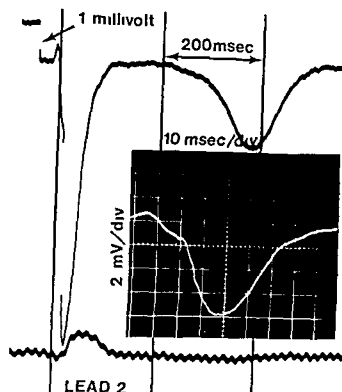


Fig 4 A poor electrogram incapable of triggering a pulse generator of conventional sensitivity Compared to Figs 2 and 3 the sharply defined intrinsic deflection is absent and in the oscilloscopic photograph the deflection is rounded rather than linear The slew rate is too slow though the electrogram amplitude is approximately 7 millivolts

Table I Ventricular endocardial unipolar electrograms

	Acute	Chronic
ID amplitude (mV)	12 4 ± 5 5	10 5 ± 4 8
ID slew rate (v /s)	2 9 ± 1 5	1 7 ± 0 86
S T elevation (mV)	4 0 ± 2 6	0 ± 0
Number of cases	77	56

Table II Unipolar endocardial atrial electrograms

ID amplitude (mV)	4 83 ± 2 21
ID slew rate (v /s)	1 18 ± 0 94
QRS voltage (mV)	2 21 ± 1 28
QRS slew rate (v /s)	0 13 ± 0 09
Number of cases	18

Table III Ventricular endocardial electrograms

	Unipolar	Bipolar
ID amplitude (mV)	12 19 ± 5 24	11 75 ± 6 02
ID slew rate (v /s)	2 82 ± 1 71	2 82 ± 0 81
ID duration (ms)	88 31 ± 30 33	61 90 ± 29 26
T wave voltage (mV)	2 41 ± 2 24	1 60 ± 1 34
S T elevation (mV)	2 62 ± 1 62	1 64 ± 1 46

rate to the atrial ID (Fig 5) Injury currents appeared in 14 per cent of acute cases (Table II) The atrial ID of the coronary sinus always occurred 40 to 60 msec after the beginning of the peripheral P wave, an important consideration during pacing involving atrial sensing Little change in either slew rate or amplitude occurred in the coronary sinus electrogram as the electrode matured

The bipolar electrogram

The bipolar signal is the result of the potential difference between two intracardiac poles each exhibiting a unipolar pattern If the bipolar axis is at right angles to the depolarization pathway, simultaneous identical signals at each pole can cancel yielding a small or zero bipolar result (Fig 6) A parallel orientation introduces a signal delay at one pole relative to the other, and can result in an augmented bipolar signal greater than either unipolar component When the proximal pole of a catheter electrode is separated from the endocardial wall its ID is small so the tip ID alone dominates the bipolar waveform Comparison of the group of ventricular bipolar and tip unipolar signals simultaneously from the same lead shows (Table III) that bipolar sensing offers

1 Either enhanced or attenuated ID s without

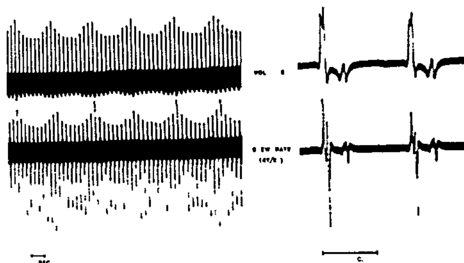


Fig 7 Respiratory effect on intrinsic deflection voltage and slew rate

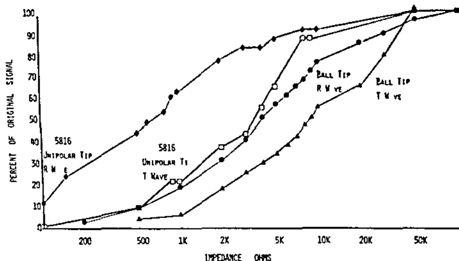


Fig 8 The effect of external shunt resistance on canine R and T wave amplitudes. Each plotted point is an average of 5 observations. The resistance at 50 per cent reduction is taken as the electrode sensing impedance

trode displacement or myocardial perforation or because the adjacent myocardium is too poor to develop an adequate electrogram Poor slew rate in combination with adequate amplitude occurs occasionally Segmenting i e direction reversal during the course of the ID may prevent sensing by a reset phenomenon in some pacemaker designs if none of the segments alone is sufficiently large and fast for triggering When multiple foci exist the electrode position should be set to sense the dominant complex disregarding or attempting to suppress unsensed foci by medication If after adequate search the best electrogram available is still too small to assure long term satisfactory sensing then a pulse generator of higher than usual sensitivity should be used

A design goal for pacemaker sensing circuits is to promote R wave transmission through compatibility of the sensing circuit with the electrode while simultaneously blocking transmission of unwanted signals Three compatibility factors are available for adjustment during manufacture sensitivity to be matched against R wave amplitude frequency response to be matched against R wave configuration and input impedance to be matched against electrode sensing impedance

A sensitivity of 2 mV the present norm is

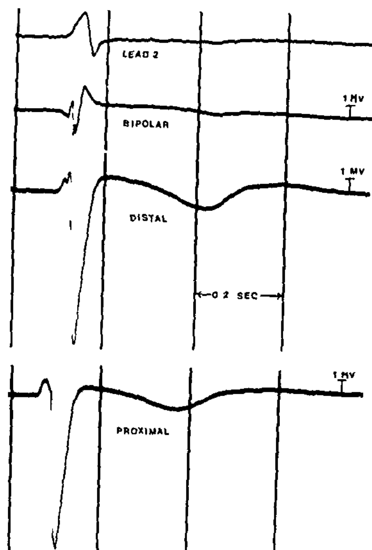


Fig 6 Two large unipolar electrograms on the electrode tip *(distal)* and ring *(proximal)* are oriented so that the resultant bipolar electrogram is too small to trigger the pacemaker Correction is accomplished by conversion to a unipolar assembly

trogram (Fig 7) probably caused by rhythmic electrode movement toward and away from the endocardium Electrogram attenuation may cause intermittent sensing failure if either amplitude or slew rate is marginal (Table IV)

Epicardial ventricular sensing signals Chronic human left ventricular electrograms were compared to those from chronic right ventricular electrodes (Table V) The left ventricular amplitude was marginally larger than from right ($p = 0.08$) The slew rate from the left ventricle is larger by a significant margin ($p = 0.05$) For chronic maintenance of adequate sensing left ventricular implant is preferable over right ventricular implant

Impedance As electrode impedance is inversely related to current density signal frequency and surface area the sensing impedance value is greater than that exhibited during stimulation The sensing impedances of five different endocardial unipolar electrodes were measured by decreasing the value of an external shunt resistance until the intracardiac R wave amplitude was half its initial value The readings ranged from 600 ohms for an 85 mm platinum electrode to 4 000 ohms for an 8 mm ^{2} elgiloy electrode (Fig 8) Since 20 000 ohms is usual for the sensing input impedance of a modern pacemaker, no more than 4 000/(4 000 + 20 000) = 17 per cent R wave attenuation is to be expected Furthermore the ID, with its higher frequency content is attenuated less than the (unimportant) far field and repolarization potentials by the frequency selective electrode impedance (in which lower frequencies are preferentially attenuated)

Discussion

Adequacy of electrode placement at implant may be judged by fluoroscopic appearance, stimulation threshold and by the sensing signal Usually the latter two parameters coincide at one anatomic position, but compromise may be necessary The amplitude of the ventricular sensing signal should be at least 2 millivolts at a slew rate of at least 1 5 millivolts per millisecond to accommodate the expected 40 per cent acute to chronic decrease A dome shaped S T segment (injury potential) of at least 2 millivolts measured at placement is a further favorable indication A high speed physiological recorder should be used ordinary ECG machines do not suffice because of limited frequency response and because the maximum 50 mm /sec paper speed renders a typical 10 millivolt 1 volt/sec ID only 0 5 mm wide too narrow for interpretation In the absence of a suitable recorder a test device designed for the purpose and available from several of the pacemaker manufacturers or an external pacemaker with adjustable sensitivity from the same manufacturer* as the pacemaker to be implanted may be used to estimate the sensing signal When bipolar sensing is unsatisfactory a remedy frequently effective is conversion to unipolar using the pole with the lower stimulation threshold (usually the tip)

Adequate sensing may be lost through elec

*As different circuits have somewhat different sensitivity use of the same manufacturer s equipment will reduce discrepancy

its relation to intrinsic deflection Am J Physiol 198 9 5 1960
Churney L and Ohshima H An improved suction electrode for recording from the dog heart in situ J Appl Physiol 19 03 1964
Geddes L A and Baker L E Principles of applied biomedical instrumentation New York 1968 John Wiley & Sons, Inc
Vermuere P and Pannier R Diagnosis of myocardial perforation by intracardiac electrograms recorded from the indwelling catheter J Electrocardiol 6 91 19 3
Parker B Electrode geometry and the evolution of long term endocardial threshold Proceedings of the ??th Annual Conference on Engineering in Medicine and Biology vol 16 Philadelphia September 19 4
8 Tarjan I Engineering aspects of implantable cardiac pacemakers, *in* Samet P, ed Cardiac pacing New York 1973 Grune & Stratton Inc
9 Pacemaker standard Labelling requirements, performance requirements, and terminology for implantable artificial cardiac pacemakers Association for the Advancement of Medical Instrumentation August 1975

adequate to detect the vast majority of ventricular signals and even most atrial signals For the remainder, 1 mV units are available When sensitivity programmable pacemakers become available, susceptibility to electromagnetic interference may be decreased by individual reduction of sensitivity and sensing of marginal electrograms improved by increase of sensitivity

The frequency responses of pacemaker sensing circuits have been empirically designed to pass the intrinsic deflection as this feature is consistently present in the electrogram of the electrode in contact with myocardium or endocardium [1] As more data become available specific frequencies can be selected for sensing or rejection Frequencies not contained in the ID may variably contain intracardiac far field repolarization, or extracardiac noise potentials and should be rejected The appearance of the ID in the electrogram stands on firm theoretical grounds, having been mathematically modelled by Wilson in 1935 The idealized intrinsic deflection has the same waveshape as those clinically observed with a near straight line segment occurring when the wavefront is closest to the electrode Further the model predicts a decrease in voltage and an increase in the waveform s duration (the net result is a lowered slew rate) as the electrode is separated from the myocardium The observed acute to chronic voltage and slew rate decreases are therefore consistent with the theory that stimulation threshold increases are caused by fibrous tissue growth about the maturing electrode [3]

Sensing amplifier input impedance has been as low as 5 000 ohms in the past but the advent of better electronic components has facilitated considerable increases However the sensing input is necessarily shunted by the stimulation circuit with its 20 000 ohm output impedance as they share the same electrode and no further net increase seems possible

The present standard (a rectangular signal) for testing sensing circuits only measures amplitude without regard to waveshape or frequency response The leading edge of a rectangular signal, rising vertically from the baseline has an infinite slew rate thus excluding it as a variable One proposed test signal improvement, a 25 Hz haversine (a single cycle of a sine wave)[4] is a poor approximation of an electrogram and yields insufficient data to characterize the frequency response The haversine contains no straight line segment (as does the ID) and more complete measurement of frequency response requires two tests in addition to amplitude, one each for the upper and lower cutoff frequencies of the sensing filter circuit Test signals in the time domain allow more realistic comparison to the electrogram Low frequency cutoff can be evaluated by a rising straight line (ramp) test signal with the slope adjusted to achieve a sensing threshold The result would be directly comparable to the maximum slew rate of the electrogram A measure of the upper cutoff frequency directly comparable to R wave duration, could be had by variation of the duration of the rectangular signal to a threshold value

The bipolar system selectively cancels far field and injury contaminants, skeletal muscle artifacts and electromagnetic interference because all these noise signals arrive simultaneously and in equal strength at both electrode poles The ID may affect the poles unequally and/or non simultaneously and be augmented rather than cancelled The net effect is an improvement in the signal to noise ratio due solely to the geometry of the sensing electrode, and distinct from further improvements that may accrue from filtering in the sensing circuit

During electrode implantation both stimulation threshold and sensing signal should be measured and recorded for future reference Proper sensing of cardiac activity is a function of the electrogram the specific characteristics of which can be determined intraoperatively of the pulse generator sensing circuit and the match, for sensing purposes of the electrode and pulse generator impedance In practice modern electrodes and pulse generators are sufficiently compatible that reliable sensing can occur even with electrodes and pulse generators of different manufacture

REFERENCES

1 Lewis T The mechanism and graphic registration of the heart beat *London 1925 Shaw and Sons Ltd*

2 Wilson F N The distribution of the currents of action and of injury by heart muscle and other excitable tissue *in* Johnston F and Lepeschkin E editors Selected *papers of Dr Frank N Wilson Ann Arbor* 1954 J W Edwards Publishing Co

3 Dower G E and Geddes M A True tran membrane potential curve from the surface of guinea pig ventricle

The basic mechanism of the hypertension observed in patients treated with beta adrenergic blocking agents would seem to be overstimulation of alpha adrenergic receptors by the excessive secretion of endogenous catecholamines unopposed by the beta adrenergic receptors, which are blocked Another possible explanation of this phenomenon may be a guanethidine-like effect of propranolol as postulated by Eliash and Weinstock, or the enhanced output of norepinephrine after nerve stimulation in the presence of high concentrations of propranolol

It is probable that the symptom complex described above may occur in any patient being treated with beta adrenergic blocking agents when subjected to a stressful situation When the hypertension is excessive alpha adrenergic blocking drugs should be administered immediately

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REFERENCES

1. Prichard B N C and Ross E J Use of propranolol in conjunction with alpha receptor blocking agents in pheochromocytoma Am J Cardiol. 18 394 1966
2. Gibson D G Pharmacodynamic properties of β adrenergic receptor blocking drugs in man Drugs 7 8 19 4
3. Atsmon A. Blum I Maoz B Steiner M and Wijsenbeck H The short term effects of adrenergic blocking agents in a small group of psychotic patients Psychiatr Neurol. Neurochir 74 251 1971
4. Atsmon A., Blum I Steiner M Latz A and Wijsenbeck H Further studies with propranolol in psychotic patients, Psychopharmacologia 27 249 1972
5. Steiner M., Blum I Wijsenbeck, H., and Atsmon A. The results of treatment with propranolol in psychosis, Kupat Holim Yearbook 2 179 1972
6. Steiner M Latz, A., Blum I Atsmon A., and Wijsenbeck H Propranolol versus chlorpromazine in treatment of psychoses associated with childbearing Psychiatr Neurol. Neurochir 76 421 1973
7. Yorkston N J., Zaki, S A Malik M K U Morrison R C and Havard C W H Propranolol in the control of schizophrenic symptoms, Br Med J 4 633, 1974
8. Rackensperger W Gaupp R Mattke D J Schwarz, D., and Stutte K H Treatment of acute schizophrenic psychosis with beta adrenergic blocking agents, Arch Psychiatr Nervenkr 219 29 1974
9. McMurtry R.J Propranolol, hypoglycemia and hypertensive crisis Ann Intern Med. 80 669 1974
10. Skinner D J., and Misbin R. I Uses of propranolol, N Engl J Med 293 1205 1975
11. Lloyd Mostyn R H., and Oram S Modification by propranolol of cardiovascular effects of induced hypoglycemia Lancet 1 1213, 1975
12. Nies, A S., and Shand D G Hypertensive response to propranolol in a patient treated with methyldopa—a proposed mechanism Clin Pharmacol. Ther 14 823, 1973
13. Juhasz Nagy A., and Szentivanyi, M Effect of alpha adrenergic coronary constriction on myocardial tissue blood flow Arch. Int. Pharmacodyn Ther 206 19 19 2
14. Eliash, S and Weinstock M Role of adrenergic neurone blockade in the hypotensive action of propranolol Br J Pharmacol. 43 287 1971
15. Werner U Wagner J and Schumann H J Effects of beta receptor blocking drugs on the output of noradrenaline from the isolated rabbit heart induced by sympathetic nerve stimulation, Naunyn Schmiedebergs Arch Pharmak. 268 102, 1971

Angina and vegan diet

A diet devoid of animal products may have certain advantages in the prevention and possible treatment of ischemic heart disease (IHD) and angina pectoris In view of this four patients with severe angina pectoris were treated with such a diet A brief summary of these patients follows

1 F W Male aged 65

Hemoglobin 12 4 Gm /dL. No ECG Cholesterol 5 7 mmol / L.

No history of coronary thrombosis, severe angina had to stop every nine or ten paces.

1/2/64	Started vegan diet Seen monthly
1/7/64	Pain much improved
2/7/64	No angina on making fairly strenuous efforts
Aug 64	Holiday in Lake District Climbed mountains no angina pain
1966	Slight cerebral thrombosis but no return of angina
1969	Another cerebral thrombosis
	Patient followed until 1974 when he died of pulmonary embolism No return of angina pectoris

2 S J S Male aged 48

Cholesterol 7.3 mmol /L. B P 140/80

25/6/67	Severe angina after walking five minutes
	Treated with Librium 10 *mg* TDS Trinitrotoluene when necessary ECG normal Continued until 18/1/68 when angina very severe Started on vegan diet and occasionally TNT
21/3/68	Condition the same Seen monthly

Annotations

Hypertension complicating treatment with beta-adrenergic blocking drugs

Treatment with beta adrenergic blocking drugs is now widely employed mainly in patients with angina pectoris or with elevated blood pressure Following the inception of symptomatic treatment of pheochromocytoma with propranolol in 1966 it was observed that in some patients there was a marked rise in blood pressure which was responsive to alpha adrenergic blocking agents[1] It was postulated that the elevation of blood pressure was caused by the secretion of both alpha and beta adrenergic agonists by the tumor the alpha agonist acting unopposed after beta adrenergic blockade (sometimes called the unmasking effect of beta blocking drugs[2])

Evidence is now accumulating that treatment with beta adrenergic blocking drugs may also cause hypertension in patients who apparently do not harbor catecholamine-secreting tumors In these patients too the hypertension may be excessive and is responsive to alpha adrenergic blocking drugs Recognition of this phenomenon and the circumstances under which it may occur is therefore of importance to the physician administering these drugs

Hypertension occurring during treatment with a beta adrenergic blocking agent was first observed by us during clinical trials carried out in the period from 1970 to 1972 in which we investigated the efficacy of high dosages of propranolol in various psychotic illnesses Well informed and written con ent was obtained from patient s nearest relative Propranolol was administered to 44 patients by mouth in rapidly increasing doses until the pulse rate dropped to 58 to 62 per minute and the blood pressure to about 90/60 mm Hg

In addition to the known side effects of propranolol there was an unexpected rise in blood pressure observed in eight patients two women and six men aged from 17 to 35 years The hypertension occurred during full beta blockade as attested by the low pulse rate which was from 58 to 62 In most of these patients the rise in blood pressure developed gradually within 3 to 4 and sometimes up to 24 hours In two patients the rise was abrupt and was accompanied by other signs of hypertensive crisis In some of them visible peripheral vasoconstriction and marked psychic tension heralded the rise in blood pressure which followed several hours later During the hypertensive phase in all patients additional symptoms were noted such as pallor and clamminess of the skin marked psychic tension and outbursts of psychomotor unrest

The elevated blood pressure responded immediately to alpha adrenergic blocking agents (phentolamine or phenoxybenzamine) and with the lowering of the blood pressure there was a concomitant abatement of the above noted symptoms (Fig 1) It is of note that there was no evident correlation between the dosage of propranolol and the rise in blood pressure since the latter occurred both at dosages as low as 600 mg /day and as high as 5 000 mg /day

Yorkston and associates[7] made observations similar to ours

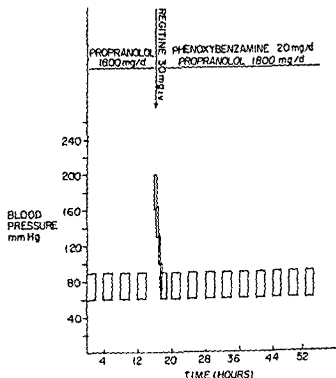


Fig 1 Response of propranolol induced hypertension to alpha adrenergic blocking drugs

when administering propranolol to schizophrenic patients in rapidly increasing dosages Rackensperger and colleagues noted the occurrence of hypertension in psychiatric patients being treated with oxprenolol

These adverse effects of beta adrenergic blockade are not specific to psychotic patients Several reports described severe hypertension during attacks of hypoglycemia in insulin dependent diabetic patients who were being treated with propranolol in doses ranging from 80 to 320 mg /day

Propranolol induced hypertension during hypoglycemia was studied by Lloyd Mostyn and Oram[11] Healthy subjects were given hypoglycemic amounts of insulin alone or insulin and 10 mg propranolol intravenously In six of the eight subjects in the second group there was an increase of the systolic and diastolic blood pressure during the hypoglycemia These investigators concluded that beta blocking drugs should not be used in diabetic patients who tend to develop hypoglycemia[4] In another patient being treated with methyldopa the intravenous injection of propranolol led to the development of hypertension and the authors postulated a stress-mediated release of a methyldopa metabolite with alpha adrenergic activity in the presence of beta blockade[11] Other studies showed that the administration of propranolol enhances the rise in peripheral and in coronary resistance caused by simultaneously infused norepinephrine

REFERENCES

1. Ellis, F R and Mumford P The nutritional status of vegans and vegetarians, Proc Nutr Soc 26 205 1967
2. Hardinge M Chambers A., Crooks H., and Stare F Nutritional studies of vegetarians III Dietary levels of fiber Am J Clin Nutr 6 523 1958
3. Miller D S and Mumford P The nutritive value of western vegan and vegetarian diets Pl. Fds Hum Nutr 2 201 19
4. Joint working party of the Royal College of Physicians of London and the British Cardiac Society Prevention of coronary heart disease J R. Coll Physicians 10 3, 19 6
5. Sanders T A. B Unpublished observations
6. Hardinge M and Stare F Nutritional studies of vegetarians nutritional physical and laboratory studies, Am J Clin Nutr 2 3 1954
Ellis F R and Montegriffo V M E Veganism, clinical findings and investigations Am J Clin Nutr 23 249 1970
8. Ellis, F R., West E and Sanders, T A B The health of vegans compared with omnivores Assessment by health questionnaire Pl Fds for Man (In press)
9. Sanders, T A B Ellis F R and Dickerson J W T Are long-chain polyunsaturated fatty acids necessary in the human diet Proc Nutr Soc 35 124A 1976.
10. Vergroesen A J Dietary fat and cardiovascular disease possible modes of action of linoleic acid Proc Nutr Soc 31 323, 1972.
11. Davies, D F., Johnson A P Rees, B W G Elwood P C and Abernethy M Food antibodies and myocardial infarction, Lancet 1 1012, 19 4
12. Scott B B Swinburne M L McGuffin P., and Losowsky M S Dietary antibodies and myocardial infarction Lancet 2 125 1976

Coronary heart disease Tests of etiological hypotheses

"Correlation does not necessarily imply causation This cri de coeur of statisticians of the R A Fisher stamp is probably known to everyone in medical research but in spite of the awareness, the maxim is often disregarded Because so many positive associations describe cause and-effect relations it is difficult to maintain one s guard and to avoid falling into the trap of assuming that all do

That coronary heart disease (CHD) correlates with cigarette smoking—at least in certain countries including the U S and U K—has been well established Many believe though some of us doubt that one or more of the products of combustion of tobacco cause or conduce to pathological changes in the coronary arteries Recently carbon monoxide has been the prime suspect

Granted that the positive association often observed between cigarette smoking and CHD allows us to propose the hypothesis cigarette smoking causes CHD how can we best proceed to test it?

The problem is complicated at the outset because in the first findings from the Seven Country study no significant correlation was found between smoking and the incidence of CHD within defined populations in Finland Italy Yugoslavia the Netherlands Crete and Corfu Some of the populations surveyed were small and a clearer picture should emerge when the final results become available Nevertheless the first findings sufficed to demonstrate that the differences in the incidence of CHD between populations could not be explained in terms of differences in the levels of smoking This is not a particularly adverse finding for the causal hypothesis it confirms what we suspect already Factors other than smoking play an important etiological role However the absence of a consistent intra population correlation between CHD and smoking—should the first findings be confirmed—presents serious difficulties for the causal hypothesis.

Studies of change in relation to time—they are secular trends—provide an obvious and even obligatory check of causal hypotheses. Do the secular trends in morbidity or mortality from CHD correlate with those for cigarette consumption? This question was recently investigated by Wald who endeavored to show that (1) recent increases in mortality from CHD in middle aged women in England and Wales have exceeded those in men and (2) this greater increase of death rates in women correlates with the larger secular increases in their recent intake of CO from cigarette smoking Unfortunately Seltzer' showed that when proper recognition is given to the changeover from the seventh to the eighth International Classification of Diseases (ICD) Wald s claim of a larger increase of mortality in women over that in men needs drastic qualification Thus for seventh ICD 420 and 422.1 the Registrar General s statistics for England and Wales show that between 1950 to 54 and 1963 to 67 recorded increases among women were markedly less than those among men in every one of the nine five year age groups from 35 to 79 years Over the entire age range 35 to 79 years the age adjusted increase among men was 31 per cent whereas among women it was only 15 per cent However for the period 1968 to 69 to 1972 to 73 and for the eighth CHD categories 410 to 414 Seltzer demonstrated three five-year age groups (out of nine) 45 to 49 55 to 59 and 60 to 64 in which the recorded increases in death rates among women did exceed those among men

It is recognized however that secular changes are often very difficult to interpret This difficulty is severe even in the instances of lung cancer and other cigarette associated cancers For no such cancer does the recorded trend in England and Wales even approximate to that expected on the assumption that changes have been due predominantly to the large increase in cigarette consumption during this century Because the strength of the association between cigarette smoking and CHD is weak relative to that for lung cancer and several other malignancies and because of the numerous other complications especially those of diagnostic consistency secular trends are unlikely to test critically the hypothesis that cigarette smoking causes CHD

Analogous difficulties arise when we attempt to interpret

11/7/68 Pain much better and could walk much further than before pain started
26/9/68 No pain
14/11/68 Started gardening and fairly heavy work without pain
ECG normal
30/1/69 No angina since
Continued on vegan diet *for nine months then* gave it up
Could not be persuaded to continue
Jan 73 Last seen when angina was beginning to recur
Patient states attacks of angina quite often and takes TNT at least twice a week

3 A F H Male aged 44

12/11/63 Small myocardial infarction ECG normal Enzymes were raised Treated with anticoagulants *B P 120/80*
Cholesterol 8 7 mmol /L Attacks of angina on exertion
Started on vegan diet
28/2/64 Condition the same
28/4/65 Less anginal pain on effort
28/5/65 No anginal pain on effort
19/8/66 Still no angina—climbs 2 000 feet up a steep mountain without pain Can walk 7 to 8 miles without pain or dyspnoea
29/8/69 Still on diet *no angina*
18 9/70 Condition as on the last date Still on vegan diet

4 R W Male aged 46

20/11/67 Severe angina on walking B P *160/105* ECG showed changes of acute infarct Cholesterol *8 3 mmol /L*
19/1/68 Started vegan diet
20/2/68 No change
21/3/68 Much better
30/4/68 No angina Has started gardening and can do quite heavy work without the onset of angina
4/2/69 Condition as on last date
6/5/69 Condition the same
29/3/74 Still on vegan diet B P 150/110

Vegans are a minority group who eat no animal produce whatsoever Their diet is similar in many respects to the typical diet consumed in developing countries where the incidence of ischemic heart disease is low Vegans tend to have a lower energy *intake than omnivores* and vegan diets tend to contain a low proportion of fat and a high proportion of unrefined carbohydrates and fiber Fat provides about a third of the total energy *in the British vegan diet* whereas in the typical *U K* omnivorous diet it provides about two fifths of the total energy Most of the fat in the vegan diet is derived from cereals nuts and oil seeds whereas in the typical U K omnivorous diet most *of the fat is derived from* milk and meat products Saturated fat provides 5 per cent and linoleic acid 13 per cent of the total energy in the British vegan diet in the omnivorous diet saturated fat provides 21 per cent and linoleic acid less than 5 per cent The vegan diet appears to be adequate provided it is comprised of a mixture of cereal legume nuts fruit and vegetable produce and is supplemented with vitamin B12

The general health of vegans appears to differ little from that of omnivores[8 9] We assessed the health of vegans and age and sex matched omnivore controls using the Cornell Medical Index and found little difference in *response except* that female vegans volunteered fewer symptoms indicative of cardiovascular disease In a later study which will soon be published in detail we investigated the incidence of a number of *risk factors associated with the development* of ischemic heart disease in vegans vegetarians and omnivores in the U K The vegans tended to have much lower serum cholesterol concentrations than the omnivores or the vegetarians we found the mean value in the vegans to be 4 1 mmol /L with a range of *3 0 to 5 4* mmol /L compared with 6 2 mmol /L with a range of 3 9 to 7 7 mmol /L The plasma phospholipid concentration also tended to be much lower in the vegans A significant proportion of the vegans had decreased proportions of *β* lipoprotein in their plasma associated with low serum cholesterol values The *incidence of raised serum triglycerides* values associated with a raised proportion of pre *β* lipoprotein in the plasma appeared to be less common in the vegans than in the omnivores and vegetarians The vegans had on average 30 per cent less body fat than the omnivores These findings suggest that British vegans but not vegetarians may be less prone to heart disease than omnivores

In our most recent study we analyzed *the long chain* polyunsaturated fatty acid *composition* of plasma and tissue phospholipids in vegan and omnivores the preliminary findings have been published and found a higher proportion of the precursor of prostaglandin E1 γ dihomolinolenic acid (20 3 ω6) and a lower proportion of the precursor of prostaglandin E3 eicosapentaenoic acid (20 5 ω3) in the ethanolamine *phosphoglycerides of the erythrocyte lipid* of the vegans compared with the omnivores This may be important as prostaglandin E1 inhibits platelet aggregation and adhesion and decreases the influence of both sympathetic and parasympathetic nerve stimulation on myocardial tissue This could well exert a beneficial effect on subjects suffering from angina pectoris and ischemic heart disease

A significant increased frequency of milk antibodies after myocardial infarction compared with controls has been reported However milk egg and gluten antibodies were not found in a more recent report There is obviously a doubt whether or not milk antibodies are concerned in the causation of IHD and further studies are needed on this point

Angina pectoris is well known for its spontaneous remissions *but it is very* unlikely that four cases would remit spontaneously Moreover there is a considerable body of evidence to suggest that a diet devoid of animal products may have certain advantages in the prevention and possible treatment of ischemic heart disease and angina pectoris We believe these findings are sufficiently significant to warrant a controlled trial to evaluate whether a diet devoid of animal *produce is effective* in treating angina pectoris

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REFERENCES

1 Ellis, F R and Mumford I The nutritional status of ve ans and vegetarians Proc Nutr Soc 26 20ɔ 1967
2 Hardinge M Chambers A Crooks H, and Stare F Nutritional studies of vegetarians III Dietary levels of fiber Am J Clin Nutr 6 523 1958
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4 Joint working party of the Royal College of Physicians of London and the British Cardiac Society Prevention of coronary heart disease J R Coll Physicians 10 3 1976
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6 Hardinge M and Stare F Nutritional studies of vegetarians nutritional physical and laboratory stud ies, Am J Clin Nutr 2 73 1954
Ellis, F R and Montegriffo V M E Veganism clinical findings and investigations Am J Clin Nutr 23 249 1970
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10 Vergroesen A. J Dietary fat and cardiovascular disease possible modes of action of linoleic acid Proc Nutr Soc 31 323, 1972
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Granted that the po itive association often observed between cigarette smoking and CHD allows us to propose the hypothesis "cigarette smoking causes CHD" how can we best proceed to test it?

The problem is complicated at the outset because in the first findings from the Seven Country study no significant correlation was found between smoking and the incidence of CHD within defined populations in Finland Italy Yugosla via the Netherlands Crete and Corfu Some of the popula tions surveyed were small and a clearer picture should emerge when the final results become available Nevertheless the first findings sufficed to demonstrate that the differences in the incidence of CHD between populations could not be explained in terms of differences in the levels of smoking. This is not a particularly adverse finding for the causal hypothesis it confirms what we suspect already Factors other than smoking play an important etiologi al role However the absence of a consistent intra population correlation between CHD and smoking—should the first findings be con firmed—p esents serious difficulties for the causal hypothe sis.

Stud es of hange in relation to time—they are secular trend pro ide an obvious and even obligatory check of causal hypotheses Do the secular trends in morbidity or mortality from CHD correlate with those for cigarette consumption? This question was recently investigated by Wald who endeavored to show that (1) recent increases in mortality from CHD in middle aged women in England and Wales have exceeded those in men and (2) this greater increase of death rates in women correlates with the larger secular increases in their recent intake of CO from cigarette smoking. Unfortunately Seltzer[4] showed that when proper recognition is gi en to the changeover from the seventh to the eighth International Classification of Diseases (ICD) Wald s claim of a larger increase of mortality in women over that in men, needs drastic qualification Thus, for seventh ICD 470 and 472.1 the Registrar General s statistics for England and Wales show that between 1950 to 54 and 1963 to 67 recorded increases among women were markedly *less* than those among men in every one of the nine five year age groups from 35 to 79 years Over the entire age range 35 to 79 years, the age adjusted increase among men was 31 per cent whereas among women it was only 15 per cent However for the period 1968 to 69 to 1972 to 73 and for the eighth CHD categories 410 to 414 Seltzer demonstrated three five year age groups (out of nine) 45 to 49 55 to 59 and 60 to 64 in which the recorded increases in death rates among women did exceed those among men.

It is recognized however that secular changes are often very difficult to interpret This difficulty is severe even in the instances of lung cancer and other cigarette associated cancers For no such cancer does the recorded trend in England and Wales even approximate to that expected on the assumption that changes have been due predominantly to the large increase in cigarette consumption during this century Because the strength of the association between cigarette smoking and CHD is weak relative to that for lung cancer and several othe malignancies and because of the numerous other complications, especially those of diagnostic con istency secular trends are unlikely to test critically the hypothesis that cigarette smoking causes CHD

Analogous difficulties arise when we attempt to interpret

11/7/68	Pain much better and could walk much further than before pain started
26/9/68	No pain
14/11/68	Started gardening and fairly heavy work without pain
	ECG normal
30/1/69	No angina since
	Continued on vegan diet for nine months then gave it up
	Could not be persuaded to continue
Jan 73	Last seen when angina was beginning to recur
	Patient states attacks of angina quite often and takes TNT at least twice a week

3 A F H Male aged 44

12/11/63	Small myocardial infarction ECG normal Enzymes were raised Treated with anticoagulants B P 120/80
	Cholesterol 8 7 mmol /L Attacks of angina on exertion
	Started on vegan diet
28/2/64	Condition the same
28/4/65	Less anginal pain on effort
28/5/65	No anginal pain on effort
19/8/66	Still no angina—climbs 2 000 feet up a steep mountain without pain Can walk 7 to 8 miles without pain or dyspnoea
29/8/69	Still on diet no angina
18/9/70	Condition as on the last date Still on vegan diet

4 R W Male aged 46

20/11/67	Severe angina on walking B P 160/105 ECG showed changes of acute infarct Cholesterol 8 3 mmol /L
19/1/68	Started vegan diet
20/2/68	No change
21/3/68	Much better
30/4/68	No angina Has started gardening and can do quite heavy work without the onset of angina
4/2/69	Condition as on last date
6/5 69	Condition the same
29/3/74	Still on vegan diet B P 150/110

Vegans are a minority group who eat no animal produce whatsoever Their diet is similar in many respects to the typical diet consumed in developing countries where the incidence of ischemic heart disease is low Vegans tend to have a lower energy intake than omnivores and vegan diets tend to contain a low proportion of fat and a high proportion of unrefined carbohydrates and fiber Fat provides about a third of the total energy in the British vegan diet whereas in the typical U K omnivorous diet it provides about two fifths of the total energy Most of the fat in the vegan diet is derived from cereals nuts and oil seeds whereas in the typical U K omnivorous diet most of the fat is derived from milk and meat products Saturated fat provides 5 per cent and linoleic acid 13 per cent of the total energy in the British vegan diet in the omnivorous diet saturated fat provides 21 per cent and linoleic acid less than 5 per cent The vegan diet appears to be adequate provided it is comprised of a mixture of cereals legumes nuts fruit and vegetable produce and is supplemented with vitamin B12

The general health of vegans appears to differ little from that of omnivores [1] We assessed the health of vegans and age and sex matched omnivore controls using the Cornell Medical Index and found little difference in response except that female vegans volunteered fewer symptoms indicative of cardiovascular disease In a later study which will soon be published in detail we investigated the incidence of a number of risk factors associated with the development of ischemic heart disease in vegans vegetarians and omnivores in the U K The vegans tended to have much lower serum cholesterol concentrations than the omnivores or the vegetarians we found the mean value in the vegans to be 4 1 mmol /L with a range of 3 0 to 5 4 mmol /L compared with 6 2 mmol /L with a range of 3 9 to 7 7 mmol /L The plasma phospholipid concentration also tended to be much lower in the vegans A significant proportion of the vegans had decreased proportions of β lipoprotein in their plasma associated with low serum cholesterol values The incidence of raised serum triglycerides values associated with a raised proportion of pre β lipoprotein in the plasma appeared to be less common in the vegans than in the omnivores and vegetarians The vegans had on average 30 per cent less body fat than the omnivores These findings suggest that British vegans but not vegetarians may be less prone to heart disease than omnivores

In our most recent study we analyzed the long chain polyunsaturated fatty acid composition of plasma and tissue phospholipids in vegans and omnivores the preliminary findings have been published and found a higher proportion of the precursor of prostaglandin E1 γ dihomolinolenic acid (20 3 ω6) and a lower proportion of the precursor of prostaglandin E3 eicosapentaenoic acid (20 5 ω3) in the ethanolamine phosphoglycerides of the erythrocyte lipids of the vegans compared with the omnivores This may be important as prostaglandin E1 inhibits platelet aggregation and adhesion and decreases the influence of both sympathetic and parasympathetic nerve stimulation on myocardial tissue This could well exert a beneficial effect on subjects suffering from angina pectoris and ischemic heart disease

A significant increased frequency of milk antibodies after myocardial infarction compared with controls has been reported However milk egg and gluten antibodies were not found in a more recent report There is obviously a doubt whether or not milk antibodies are concerned in the causation of IHD and further studies are needed on this point

Angina pectoris is well known for its spontaneous remissions but it is very unlikely that four cases would remit spontaneously Moreover there is a considerable body of evidence to suggest that a diet devoid of animal products may have certain advantages in the prevention and possible treatment of ischemic heart disease and angina pectoris We believe these findings are sufficiently significant to warrant a controlled trial to evaluate whether a diet devoid of animal produce is effective in treating angina pectoris

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well as of the etiology pathophysiology and natural history of disease, is necessary Experience is of utmost importance—years of experience with careful unbiased follow up of clinical performances gathered from practice Just as practice makes a good pianist so experience and practice of medicine make a good clinician. To exercise clinical logic is not possible for technocrats. They are usually a one technic technician The history and physical examination require plenty of time with the patient and his family time is indispensable and is limited. To merely lance a boil does not establish medical ability But to study and advise a patient and his family to the entire family's best interest requires a master clinician who really knows people likes people likes medical practice and enjoys helping the sick. Sickness can be extremely upsetting to a family—curing and helping the sick with consideration for the entire family can be most gratifying especially to the compassionate physician. The clinician who is dedicated to the practice of medicine and who adheres to the Golden Rule and puts patients and their best interests on a par with his own, or above his own renders the greatest service to the sick. The routine request for laboratory data special procedures tests, "blood gases," respiratory function studies treadmill exercise tests, echocardiography vectorcardiography angiography nuclear scans, endoscopic studies consultations galore to mention only a few is not right nor to the best interest of patients This type of "routine study" reflects economic interests and lack of clinical knowledge clinical logic and adequate consideration for the sick man's dollar This practice may proceed under the guise of "good practice" it may be impressive to the patient, but it is expensive to him and to his insurance and governmental supporting agencies. Only necessary laboratory data are required and should be requested. Hazardous studies should be limited to patients in whom there is a definite need

There is a need for more clinical logicians—master clinicians. Few patients ever get to see one there are so few available But when the patient consults a master clinician he fully appreciates the difference and immediately recognizes the real doctor The schools of medicine and medical societies need to take cognizance of the new practice" Massive quantities of unnecessary data do not reflect knowledge of medicine or good practice To observe the request of laboratory data which logically support the clinical needs of a masterfully obtained history and physical examination is a delight. Shotgun" data are worthless—high in mass but low in thought And to have no data is better than to have wrong data

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secular trends in populations such as British doctors from 1951 to 1965 in which cigarette consumption was falling[6] Studies of self selected populations such as those British doctors who elected to answer Hill and Doll s questionnaire raise futher problems because reponders and nonresponders were not selected randomly The bias of self selection has been clearly demonstrated[6] Standardized death rates for responders and non responders differed throughout the first 15 years of the study but the contrasts were especially large during the first three years[6]

Comparisons between a group such as British male doctors and the general male population of England and Wales are fraught with danger because of differences in diagnostic standards life style education and perhaps genetic factors When ex smokers are followed as a group the phenomenon of self selection poses even more intractable problems of interpretation There are many possible reasons both for giving up and for continuing to smoke any one of these might be associated directly or indirectly and positively or negatively with the risk of CHD In any case causal and constitutional (genetic) hypotheses make similar predictions where ex smokers are concerned Obviously the causal hypothesis predicts falling rates of CHD among ex smokers Less obviously the constitutional hypothesis makes a similar prediction those who give up smoking will tend to be social smokers rather than the genetically predisposed dependent smokers who by hypothesis tend also to be genetically predisposed to CHD

How then can we distinguish reliably between causal and genetic interpretations of positive associations?

Elsewhere I have argued with certain reservations that studies of twins discordant for smoking habits should eventually yield the most critical evidence for testing causal constitutional and combined hypotheses The main practical hindrance to such studies is small numbers Monozygotic twin pairs tend to be strikingly concordant for smoking habits Nevertheless surveys of angina pectoris in 1 200 Swedish and 4 000 U S male twin pairs and of mortality from CHD in Swedish twins are beginning to yield some tentative indications In the most recent study[8] of the U S male twins the relative risk of angina in the twin population as a whole for smokers versus non smokers was found to be 1 7 which agrees well with other studies of morbid and fatal CHD in large populations of male singletons Among 426 monozygotic (MZ) pairs discordant for smoking 11 smokers and 12 non smokers had angina and among 620 discordant dizygotic (DZ) pairs 19 smokers and 10 non smokers were affected The constitutional theory predicts equality of prevalence among smoking and non smoking members of a series of MZ discordant twins and a higher prevalence in the smoking members of DZ discordant pairs The causal theory predicts a higher prevalence among the smokers than among the non smokers in both MZ and DZ twin pairs discordant for smoking Numbers in this latest survey are still too small to discriminate effectively between causal and constitutional theories but they corroborate the earlier findings for angina and fatal CHD in Swedish twins

In view of the uncritical nature of other kinds of evidence we have little option but to conclude that the identification of cigarette smoking as a causal factor in CHD is premature Further studies of discordant twins on the widest possible international basis could help to reduce the area of uncertainty

New investigations using twins should be undertaken to find whether other environmental "risk factors—and especially dietary ones such as eggs saturated fats and dairy produce—are causally related to CHD It would not be surprising if such tests should prove to be even more difficult than the one discussed above in connection with cigarette smoking But it would be most unfortunate if the consumption of such staple and relatively inexpensive items of diet were to be discouraged on the basis of untested assumptions about the etiology and pathogenesis of CHD

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REFERENCES

1 Keys A (Editor) Coronary heart disease in seven countries Circulation **41**(Suppl 1) I 1 1970
2 Wald M J Mortality from lung cancer and coronary heart disease in relation to changes in smoking habits Lancet **1** 136 1976
3 Seltzer C C Mortaltiy from lung cancer Lancet **1** 741 1976
4 Burch P R J The biology of cancer A new approach Medical & Technical Publishing Lancaster England 1976 University Park Press Baltimore
5 Seltzer C C Critical appraisal of the Royal College of Physicians report on smoking and health Lancet **1** 243 1972
6 Doll R and Pike M C Trends in mortality among British doctors in relation to their smoking habits J R Coll Physicians Lond **6** 216 1972
7 Fisher R A Smoking The Cancer Controversy Edinburgh 1959 Oliver & Boyd
8 Hrubec A Cederlof R and Friberg L Background of angina pectoris Social and environmental factors in relation to smoking Am J Epidemiol **103** 16 1976
9 Cederlof R Friberg L Jonsson E and Kaij L Respiratory symptoms and angina pectoris in twins with reference to smoking habits An epidemiological study with mailed questionnaire Arch Environ Health **13** 726 1966
10 Friberg L Cederlof R Lorich U Lundman T and de Faire U Mortality in twins in relation to smoking habits and alcohol problems A study on the Swedish Twin Registry Arch Environ Health **27** 294 1973

Of clinical data

The study of a patient is an exercise in clinical logic This can only be performed well by a professional experienced master clinician with an extensive background of knowledge who can obtain and use reliable data to arrive at a *logical* conclusion A thorough knowledge of pathology anatomy physiology history taking physical examination and pharmacology as

of acute myocardial infarction Am. Heart J 93 603, 19—

2. Prinzmetal M Fkmekci A Kennamer R et al Variant form of angina pectoris a previously undelineated syndrome J.A.M.A 174 1794 1960
3. Robinson J S Prinzmetal's variant angina Am Heart J 70 97 1965
4. Laks M Dahlgren J and Mandel W J The dynamic ECG in the diagnosis of variant angina pectoris J Electrocardiol. 7(1) 93 19 4
5. Golding B Wolf E Tzivoni D and Stern S Transient S-T elevation detected by 24 hour FCG monitoring during normal daily activity Am Heart J 86 501 1973
6. Chi he P and Haiat R Tran ient ST segment elevation occurring without anginal pain Correlations with Prinzmetal's angina J Electrocardiol. 8(3) 275 1975
7. Madias, J E Madias, N E and Hood W B Jr Precordial ST-segment mapping 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction Circulation 1976 (In press)

Truncus Arteriosus Communis eleven years later

To the Editor

In 1965 Richard and Stella Van Praagh stated that Truncus Arteriosus Communis (TAC) is a pulmonary infundibular atresia associated with an aortico pulmonary septal defect and included in the spectrum of the tetralogy of Fallot The same embryological definition is proposed in the recent cooperative study by Calder and associates

In the eleven years that have passed between these two reports TAC came into the field of radical surgical management In addition perhaps owing to the previous definition of Van Praagh surgeons placed pulmonary atresia with ventricular septal defect and TAC in the same group since both defects are characterized by a discontinuity between heart and pulmonary vasculature

Based upon our anatomical study of TAC hearts and in the light of recent fundamental contributions regarding development of the conus cordis and its pathology we are perplexed by this definition of TAC In accord with earlier theories we consider TAC a single undivided conotruncus, i.e. a malformation characterized mainly by failure in septation of the cardiac outflow tracts and semilunar valves

We reached this conclusion for the following reasons

1 Van Praagh considers as TAC type B also the large aorto-pulmonary septal defects in which a normal pulmonary infundibulum is present

2 If a pulmonary infundibular atresia characterizes TAC type A a few specimens should exist in which even a blind pulmonary infundibulum can be identified as a separated entity from the sinus of the right ventricle such as seen in pseudotruncus arteriosus To our knowledge similar findings have not been reported

3. Pathological evidence has been furnished for the existence of TAC cases with normally divided ventricular infundibula and a common semilunar valve owing to isolated failure of growth of the truncal septum This feature suggests a pectrum of septation defects with possible isolated absence of conal, truncal and aorto pulmonary septa

4 Our report of a TAC specimen showing persistence of the conoventricular flange which determines a mitro-truncal fibrous discontinuity demonstrates that the parietal conus can be normally present [10] The lack of division of the primitive truncoconus is the essential growth defect despite the variable anatomy of the free wall of the conus.

Van Praagh revised his definition of transposition from "mitro-pulmonary fibrous continuity" into "great arteries transposed across the ventricular septum" when he discovered transposition with bilateral conus and transposition with posterior aorta We should like to know whether he still maintains his opinions on truncus in the light of these considerations.

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REFERENCES

1. Van Praagh, R., and Van Praagh S The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications A study of 57 necropsy cases, Am J Cardiol 16 406 1965
2. Calder L Van Praagh R., Van Praagh S Sears W F Corwin R. Levy A., Keith J D and Paul, M H Truncus Arteriosus Communis Clinical angiocardiographic and pathologic findings in 100 patients Am Heart J 92 23 1976
3. Thiene G Bortolotti U Gallucci V., Terribile V., and Pellegrino P A Anatomical study of truncus arteriosus communis with embryological and surgical considerations, Br Heart J 38 1109 19 6.
4. Goor D A Dische R., and Lillehei, C W The conotruncus I Its normal inversion and conus absorption Circulation 46 37 1972
5. Goor D A and Edwards, J E The spectrum of transposition of the great arteries with specific reference to developmental anatomy of the conus Circulation 48 406 1973
6. Anderson R H Wilkinson J L., Arnold R., and Lubkiewicz, K. Morphogenesis of bulboventricular malformations I Considerations of embryogenesis in the normal heart Br Heart J 36 242, 19 4
7. Anderson R H Wilkinson J L., Arnold R Becker A E and Lubkiewicz K Morphogenesis of bulboventricular malformations II Observations on malformed hearts, Br Heart J 36 948 1974
8. Collett R W and Edwards J E Persistent truncus arteriosus A classification according to anatomic types Surg Clin North Am 29 1245 1949
9. Rosenquist G C Bharati S McAllister H A., and Lev M Truncus arteriosus communis truncal valve anomalies associated with small conal or truncal septal defects, Am J Cardiol. 37 410 19 6.
10. Thiene G Cucchini F., and Pellegrino P A Truncus arteriosus communis associated with underdevelopment of the aortic arch Br Heart J 37 1268 1975
11. Van Praagh, R Vlad P and Keith J D Complete transposition of the great arteries in Heart disease in infancy and childhood 2nd ed Keith J D Rowe R D and Vlad P eds New York 1967 Macmillan Publishing Co Inc chap 25
12. Van Praagh, R Perez Trevino C Lopez Quellar M., Baker F W Zuberbuhler J R Quero M Perez V M Moreno F and Van Praagh, S Transposition of the great arteries with posterior aorta anterior pulmonary artery subpulmonary conus and fibrous continuity between aortic and atrioventricular valves Am J Cardiol. 28 621 1971

Letters to the Editor

ST T segments in ischemic heart disease

To the Editor

The experience of Drs Stern and Tzivoni[1] with Holter *monitoring techniques in patients with proved or suspected* coronary artery disease is exciting and thought provoking

I share their belief that the ST segment is a portion of the ECG curve subjected to downward and upward swings some of which can be explained by concomitant changes in the clinical picture or other objective parameters and some not

Changes of the magnitude of ST segment elevation for *example* in patients with myocardial infarction can be often explained by the occurrence of transient or prolonged chest pain[2] following ventricular fibrillation or during recovery from pulmonary edema[3] Occasionally *marked shifts in the* degree of ST segment elevation are not explainable with the *currently utilized clinical monitoring* parameters[4] *Although* blood pressure and heart rate can be serially measured and the clinical picture closely observed there must be variables (currently beyond our reach) which modulate the moment to moment status of balance of oxygen supply and demand and *its ECG expression*

It is interesting that the dynamic ECG revealed increase stability or decrease in ST segment depression during sleep in previous work of the authors Also different gradations of ST segment depression (unpredictable in degree) were produced by *daily events conventionally thought to be pro* vocative of myocardial ischemia as walking postpradial state *and mental stress The transient character* of some of these marked ST segment depressions is often encountered in the hospital where patients are found to have fast resolution of ECG alterations with the initial *suspicion of the diagnosis* of myocardial *necrosis often not substantiated*

In regard to the authors thought about the presence of stimuli which are more capable in provoking ECG evidence of myocardial ischemia than physical *effort* there is verification by inference available from the cardiac clinic where patients often complain of chest discomfort during periods of emotional upset rather than during times of vigorous physical exertion Such occurrences confirm the importance of comple *menting the exercise tests with Holter monitoring in the* evaluation of patients suspected of having myocardial ischemia

The dynamic nature of ST segments has been implicated to explain their stability when treadmill stress fails to produce ST-segment depression in patients with known ischemic heart disease On such an occasion a ventricular aneurysm causing a *cancelling ST segment elevation may* neutralize (it is theo rized) the ST segment depression *of myocardial ischemia*

The advent of dynamic electrocardiograhy has provided a mechanism for exposing the dynamic character of ST segment in patients with heart disease The experience of the authors *with* continuous ECG recordings coupled with detailed clin ical information will certainly contribute to the identification of many *mechanisms altering* the ST segment

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REFERENCES

1 Stern S and Tzivoni D The dynamic nature of the ST T segment in ischemic heart disease AM HEART J 91 820 1976
2 Madias J E Use of precordial ST-segment mapping AM HEART J (In press)
3 Madias J E and Hood W B Jr Precordial ST segment mapping 3 Stability of maps in the early phase of acute myocardial infarction AM HEART J 93 603 1977
4 Radvany P Maroko P R and Braunwald E Effects of hypoxemia on the extent of myocardial necrosis after experimental coronary occlusion Am J Cardiol 35 795 1975
5 Stern S, and Tzivoni D Dynamic changes in the ST T segment during sleep in ischemic heart disease Am J Cardiol 32 17 1973
6 Manvi K N and Ellestad M H Elevated ST segments with exercise in ventricular aneurysm J Elec trocardiography 5 317 1972

Reply

To the Editor

We appreciate very much the comments of Dr Madias concerning our observations on the dynamic nature of the ST T segments He and Dr Hood using the technique of precordial ST segment mapping elegantly demonstrated *transient elevation of the ST segment concomitant* to chest pain which follows ventricular fibrillation or pulmonary edema in patients with acute myocardial infarction The authors describe alterations in the degree of ST segment elevation at different times and a small but statistically significant decline in the number of sites showing ST elevation when the mapping was repeated after an hour It should be *added that transient upward shifts of* the ST *segment* under conditions other than acute myocardial infarction were already noted in patients with Prinzmetal s angina neuro circulatory asthenia during sleep and although most authors agree that subepicardial ischemia is the most plau sible mechanism leading to this phenomenon in most instances this may not be the only cause Dynamic changes in *the ST segment* were convincingly demonstrated in another study of the authors by finding a reduction in the number of areas showing ST *elevation after oxygen administration to* patients with acute myocardial infarction a change reversed on return to ambient air breathing[1]

Dr Madias and co workers made a valuable contribution to the subject of the dynamic nature of the ST T segment by using the method of serial precordial ST segment mapping Certainly the new methods which come to inspect and follow the patient (and his *electrocardiogram*) in a more intensive and meticulous way will provide more detailed and exact information in the future about this *interesting subject*

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REFERENCES

1 Madias J E and Hood W B Jr Precordial ST segment mapping 3 Stability of maps in the early phase

graphic findings in TAC were studied with considerable care and it was not rare to find in the lateral projection what looked like a small blind infundibular outlet chamber Contrast material demonstrated this blind recess and the catheter tip might lodge in it Fig 4b of Calder and associates shows such an infundibular recess but only moderately well because we did not have this point in mind when selecting this angiocardiogram However I agree that we have not seen a *well defined* atretic infundibular chamber as one may see in some cases of tetralogy with pulmonary outflow tract atresia In our experience the right ventricular outflow tract recess in TAC is not as well defined as that This is why Victorica and co-workers[8] concluded that TAC is characterized by *absence* of the infundibulum—not by an infundibular septal defect but by absence of the infundibulum To reiterate we think that in typical TAC the subpulmonary infundibulum is atretic (not absent) (1) because of the absence of pulmonary-mitral fibrous continuity in cases of TAC with a pulmonary leaflet remnant and (2) in view of the destruction of the pulmonary valve that would not be wiped out if the subpulmonary infundibulum were absent as in typical TGA

4 *Anatomy first and embryology second* We think that pathologic anatomic findings—*all* of them—should come first and that embryologic hypotheses should come second not vice versa Inconvenient anatomic findings cannot be over looked, merely to support one s cherished embryologic hypothesis! We have endeavored to practice what we preach. Dr Thiene is right that we revised our definition of TGA from a relatively well-developed muscular subaortic infundibulum"[9] to aorta arising above the morphologically right ventricle and pulmonary artery originating above the morphologically left ventricle We felt that this change was essential in order for the definition of TGA to be consistent with *all* of the known well documented anatomic data [10]

It may be said that science is the only orthodoxy that thrives on perpetual revision Surely it is axiomatic that we all must be prepared to revise old concepts when th y are found not to be consistent with all of the known well documented data The classical concept of TAC mentioned by Dr Thiene is not consistent with the anatomic findings—not even in typical cases Consider for example the truncal valve typically it should be quadricuspid and the pulmonary valve should not be largely or totally obliterated if the classical concept of TAC were correct

In conclusion there is no doubt that we all have much to learn, and I would again like to thank Dr Thiene for his stimulating commentary

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REFERENCES

1 Van Praagh R and Van Praagh S The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications a study of 57 necropsy cases Am J Cardiol 16 406 1965
2. Calder L. Van Praagh, R., Van Praagh S Sears, W P., Corwin R Levy A., Keith J D and Paul M H Truncus Arteriosus Communis Clinical angiocardiographic and pathologic findings in 100 patients, AM HEART J 92 23 1976
3 Lev M and Saphir O Truncus arteriosus communis persistens J Pediatr 20 74 1942.
4 Collett R W and Edwards, J F Persistent truncus arteriosus a classification according to anatomic types, Surg. Clin North Am 29 1245 1949
5 Manhoff L J and Howe J S Absence of the pulmonary artery a new classification for pulmonary arteries of anomalous origin Report of a case of absence of the pulmonary artery with hypertrophied bronchial arteries, Arch. Pathol. 48 155 1949
6. Van Praagh R Classification of Truncus Arteriosus Communis (TAC) AM HEART J 92 129 1976
7 Keck, E W Roloff D., and Markworth P Cardiovascular findings in children with the thalidomide dysmelia syndrome Proc Assoc Eur Paediatr Cardiol. 8 66 1972.
8 Victorica B E Krovetz L J Elliott, L P., Van Mierop L H S Bartley T D Gessner I H and Schiebler G L Persistent truncus arteriosus in infancy AM HEART J 77 13 1969
9 Van Praagh R Vlad P., and Keith, J D Complete tran position of the great arteries *in* J D Keith R. D Rowe and P Vlad *Heart disease in infancy and childhood* 2nd edition New York 1967 Macmillan Publishing Co Inc p 687
10 Van Praagh, R Pérez Trevino C., Lopez Cuellar M., Baker F W Zuberbuhler J F Quero M., Pérez V M Moreno F and Van Praagh S Transposition of the great arteries with posterior aorta anterior pulmonary artery subpulmonary conus and fibrous continuity between aortic and atrioventricular valves Am J Cardiol. 28 621 1971
11 Van Praagh R Transposition of the great arteries II Transposition clarified Am J Cardiol 28 739 1971
12. Warkany J Cited in Ref 6 Van Praagh R AM HEART J 92 No 2 1976 p 130

Reply

To the Editor

I would like to thank Dr Thiene for his interesting questions and comments concerning truncus arteriosus communis (TAC)

1 *Definition* Dr Thiene states that in 1965 we made an embryological definition of TAC and that this same embryological definition is proposed in the recent study by Calder and associates This is not true Our *definition* of TAC has never been embryologic It has always been anatomic In 1965 we wrote[1] The criteria of Lev and Saphir[2] were employed for the anatomic diagnosis of truncus arteriosus (1) only one great artery arises from the base of the heart and (2) this great artery gives rise to the coronary arteries to the pulmonary arteries and to the systemic arteries This definition excludes type 4 truncus of Collett and Edwards (one arterial trunk without pulmonary arteries the lungs being supplied by bronchial arteries or other collaterals) This anomaly is considered to be a solitary aorta with absence of the pulmonary artery and its branches not a common aortico pulmonary trunk

Recently Calder and colleagues[3] stated Truncus arteriosus communis is defined as a congenital cardiovascular malformation in which one great artery arises from the base of the heart and gives origin to the coronary pulmonary and systemic arteries

Thus our definition was and remains the classical anatomic definition of TAC Moreover we think it is an *important principle* that congenital heart disease be defined anatomically not embryologically This is because embryologic hypotheses are very prone to change whereas the pathologic anatomy is relatively stable

2 *Embryologic interpretation* This is what Dr Thiene is talking about not definition

Yes we still think that typical TAC (such as types A1 and A2) appears to result from infundibular atresia with partial or complete absence of the pulmonary valve leaflets and with partial or complete absence of the aorticopulmonary septum Hence we think that typical TAC is closely related to tetralogy of Fallot with pulmonary outflow tract atresia (pseudotruncus) The probability of a developmental relationship between TAC and tetralogy is supported not only by the morphologic similarities but also by the high incidence of right aortic arch in both anomalies and also by the thalidomide experience Warkany[1] and Keck and co workers[5] have found that tetralogy of Fallot and TAC predominated among the anomalies of the great arteries in infants with the thalidomide syndrome

However as I have recently stated TAC certainly seems to be a phenotype not a genotype As defined in the usual anatomic way as we have done TAC certainly seems to include several very different diseases when viewed from the embryologic standpoint[6] For example TAC with an intact ventricular septum is very different from typical TAC So is TAC with interrupted aortic arch and so is TAC with a complete muscular subtruncal infundibulum—that we too have observed[6]

Dr Thiene appears to have accepted the classical embryological interpretation of TAC a single undivided conotruncus e a malformation characterized mainly by failure in septation of the cardiac outflow tracts and semilunar valves

Theoretically, I have no reason for not accepting this classical embryological interpretation However the problem is that all of the known well documented anatomic data do not fit this interpretation What about cases with an intact ventricular septum?[7,8] Why is TAC with a quadricuspid truncal valve not more frequent? Why when a quadricuspid valve is present does the truncal valve appear to be composed of the aortic valve plus a pulmonary leaflet remnant?

In other words, if the classical hypothesis were correct one would expect typically to find (1) a truncal valve composed of four leaflets and (2) this quadricuspid truncal valve should be made up of the undivided aortic and pulmonary valves But that is not what one doe find Typically the truncal valve is tricuspid and the truncal valve appears to be the aortic valve[1] In other words the pulmonary valve appears to have been destroyed or not to have formed One typically does not find both the pulmonary and the aortic valves that are in common—not separated from each other by the truncal septum If the truncal valve is quadriscuspid one typically finds a solitary remnant of the pulmonary valve a single leaflet that may be longer and taller than the other three (aortic) leaflets all three of which are very nearly the same size as in a normal aortic valve One does not find three pulmonary leaflets that simply have not been separated from the three aortic leaflets

Why not? What happens to the pulmonary valve in typical so called truncus arteriosus communis? What destroys the pulmonary valve or only permits persistence of a pulmonary leaflet remnant? We think that the answer in typical TAC is pulmonary infundibular atresia—not agenesis but atresia In our experience the pulmonary leaflet remnant has never been in direct fibrous continuity with the atrioventricular valves By contrast in typical transposition of the great arteries (TGA) absorption of the subpulmonary infundibular free wall results in pulmonary-mitral fibrous continuity Thus in TAC if the subpulmonary infundibulum failed to form or were absorbed one would expect (1) a tricuspid pulmonary valve (not an obliterated pulmonary valve as in tetralogy with pulmonary infundibular atresia) and (2) pulmonary-atrioventricular fibrous continuity—as in typical TGA

Upon careful inspection of the right ventricular outflow tract we found that we could not tell typical TAC from tetralogy with pulmonary outflow tract atresia without looking at the great arteries[1]

So our conclusions [6] have been based on the pathologic findings rather than on embryologic theory

We think the assumption that TAC as classically defined is only one embryologic abnormality is not supported by the pathologic anatomic findings Such an assumption is a remarkable act of faith[1] However if *all* of the known and well documented anatomic data did appear to support this classical interpretation we would immediately agree However all of the known and well documented anatomic data are *not* consistent with the classical interpretation which is the point

3 *Pulmonary infundibular atresia* Dr Thiene said If a pulmonary infundibular atresia characterizes TAC type A a few specimens should exist in which even a blind pulmonary infundibulum can be identified as a separate entity from the sinus of the right ventricle such as seen in pseudotruncus arteriosus To our knowledge similar findings have not been reported In the investigation by Calder[3] the angiocardio

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Book reviews

Ventricular Function At Rest and During Exercise Edited by H Roskamm and Ch Hahn New York 1976 Springer Verlag 183 pages Price $14 80

This publication represents the proceedings of an international symposium held in Geneva October 15 to 17 1975 The subjects discussed are extensive and varied These include the relationship of cardiac ultrastructure and function physiologic determinants of ventricular function muscle and pump function of the mammalian heart coronary blood flow at rest and with exercise ventricular function during exercise with infarction and stress and with digitalis as well as many other aspects of ventricular function in health and disease This paperback publication contains brief reports which are more like abstracts rather than detailed critical presentations of studies The reports are in English and German The papers are so brief that the reader finds it difficult to evaluate the quality of the studies and data This is not a very good publication except that it does summarize briefly the presentations made at the conference All presentations do not represent a critical review of the subject of ventricular function

Noninvasive Evaluation of Human Circulation *By J Somonyi* M D C Sc Budapest 1976 Akademiai Kiado 250 pages Price $15 00

This book is quite different from any written on the study of the heart without the use of cardiac catheterization The emphasis is on curve analysis analysis of such tracings as the arterial pulse wave the heart sound tracing and other recordings that may be obtained externally For example there are chapters on the first derivation of the external carotid tracing and its use to semiquantitatively and quantitatively measure inotropic phenomena the analysis of the sound tracings also to quantitate inotropic activity exercise stress studies computer analysis discriminant analyses and others Recordings of pulsatile phenomena and heart sounds have been exhaustively analyzed in the past by many investigators This book adds little if anything to the clinical study of the heart This book is not of use to clinical cardiologists Physiologists will find the book interesting

The Nervous System in Arterial Hypertension Edited by Steve Julius M D Sc D and Murray D Esler M B B S Ph D *Springfield Ill 1976 Charles C Thomas Publisher* 476 pages Price $17 50

This book represents the proceedings of a conference held in Ann Arbor during February 1974 The sections include papers concerned with the neurogenic component of spontaneous hypertension in rats models of neurogenic hypertension mechanoreceptors human hypertension and antihypertensive drugs The many brief papers review some of the present states of knowledge concerning the relationship of the central and peripheral nervous systems to arterial hypertension The discussions are good The important role of the nervous system in hypertension is well accepted This book very clearly reviews some of the studies in progress related to the nervous system and hypertension Experimental approach to neurogenic factors in human hypertension are difficult but as indicated in this publication these nervous factors must be considered at all times especially in clinical therapy The action of the antihypertensive agents reflect this very well This is a good book

Progress in Hemostasis and Thrombosis vol 3 *Edited by* Theodore H Spaet M D New York 1976 Grune & Stratton Inc 342 pages

The importance of hemostasis and thrombosis in clinical medicine is well recognized Thrombosis and embolism are constant problems which plague the clinician and injure and kill his patients This third volume on the subject reviews aspects of problems related to thrombosis Most of the discussions are concerned with studies directed at a better understanding of hemostasis and thrombosis e g platelet adhesion structure of fibrinogen factor V and biology of megakaryocytes The clinical aspects of the thrombosis are discussed very little This is proper in view of the fact that clinical discussions of hemostasis and thrombosis have been extremely repetitive in recent years and very few clinical advances have been made This is a good book in which the more fundamental molecular aspects of hemostasis and thrombosis are presented

Books received

Adhering to Medical Regimens ***Pilot Experiments in Patient*** **Education and Social Support** By Robert D Caplan Eliza beth A R Robinson John R P French Jr John R Caldwell and Marybeth Shinn *Ann Arbor 1976 Institute for Social* Re earch The University of Michigan Press 267 pages Price $10 00

Psychological Aspects and Physiological Correlates of Work and Fatigue Compiled and edited by Ernst Simonson M D and Philip C Weiser Ph D Springfield Ill Charles C Thomas Publisher 417 pages Price $38 50

Myocardial Infarction Community Registers Public Health in Europe No 5 World Health Organization Copenhagen 1976 *WHO 223 pages*

Cerebral Arterial Disease Edited by R W Ross Russell New York 1976 Churchill Livingstone 316 pages Price $30 00

Neuromuscular Mechanisms for Therapeutic and Conditioning Exercise Edited by Howard G Knuttgen Ph D Baltimore 1976 University Park Press 134 pages Price $7 95

Atrioventricular Canal Defects Edited by Robert H Feldt M D Philadelphia 1976 W B Saunders Company 145 pages Price $22 50

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